Practically meeting modified release BE requirements

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To bear in Remembrance...

Whenever a theory appears to you as the only possible one, take this as a sign that you have neither understood the theory nor the problem which it was intended to solve.

Karl R. Popper

Even though it's *applied* science we're dealin' with, it still is – *science!*

Leslie Z. Benet

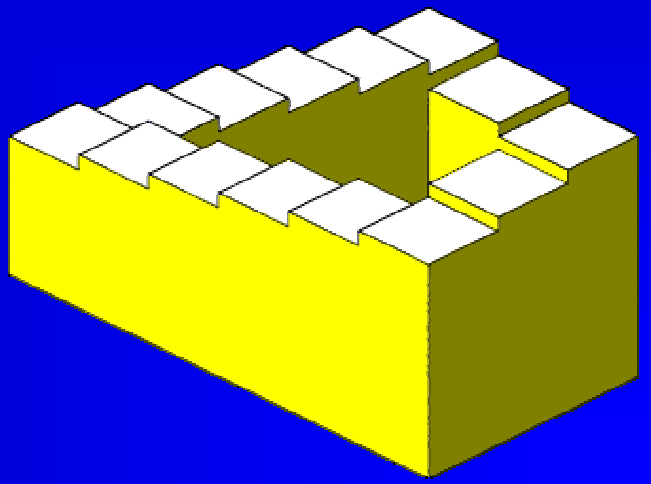
***Statistics* – A subject which most statisticians find difficult but in which nearly all physicians are expert.**

Stephen Senn

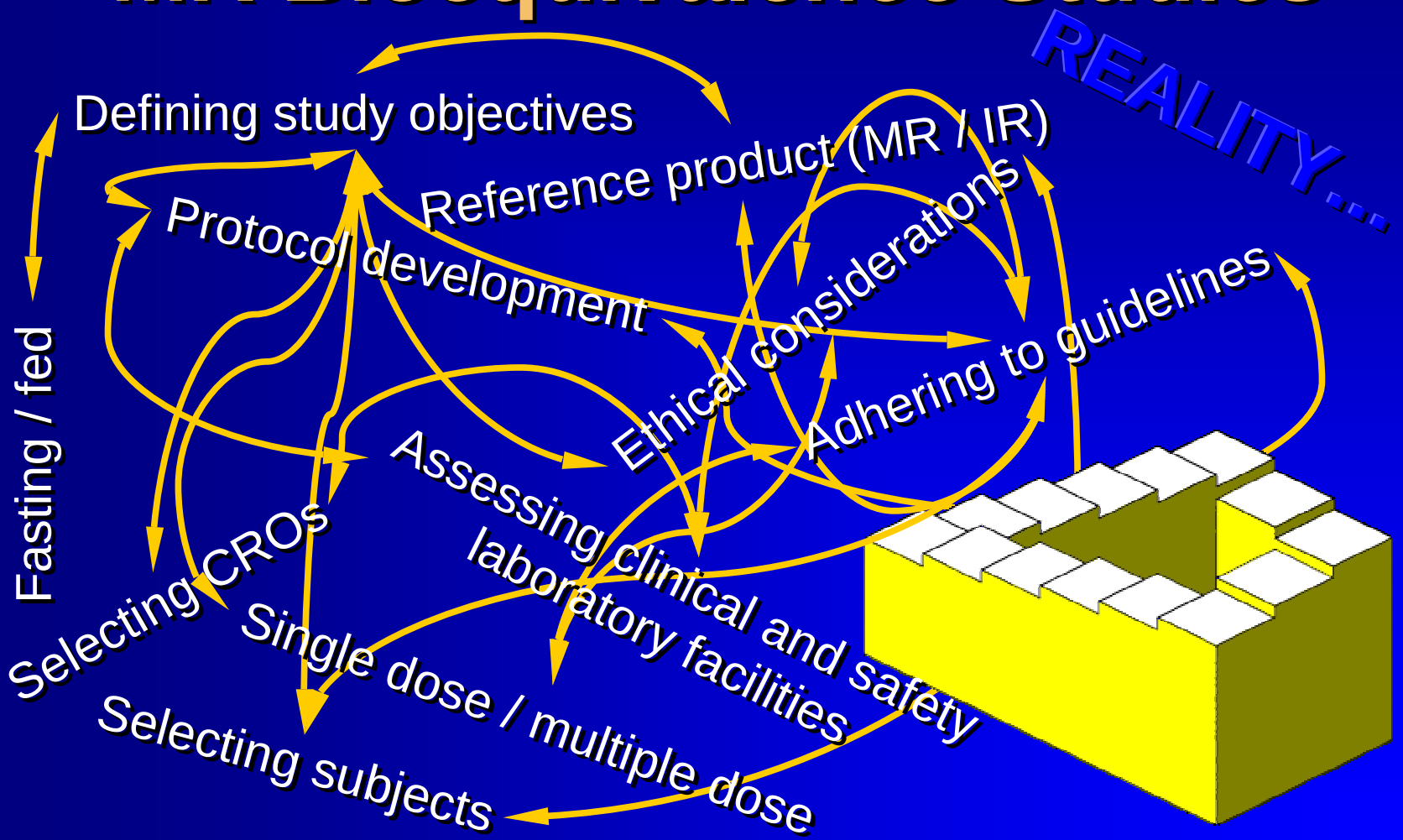
MR Bioequivalence Studies

DREAM...

- Defining study objectives
- Fasting / fed
- Single dose / multiple dose
- Reference product (MR / IR)
- Selecting CROs
- Protocol development
- Ethical considerations
- Assessing clinical and safety laboratory facilities
- Selecting subjects
- Adhering to guidelines



MR Bioequivalence Studies



Some topics…

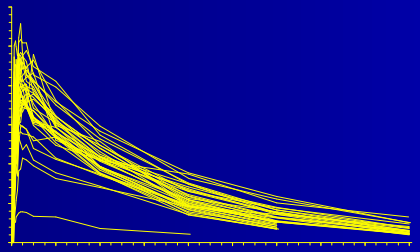
- Bioequivalence
  - Surrogate of clinical equivalence or
  - Measure of pharmaceutical quality?
- Types of studies
  - Pharmacokinetic (PK)
  - Pharmacodynamic (PD)
  - Clinical (equivalence and/or safety/efficacy)
  - Healthy Subjects *vs.* patients
  - Single dose *vs.* multiple dose
  - Parallel / cross-over / replicate

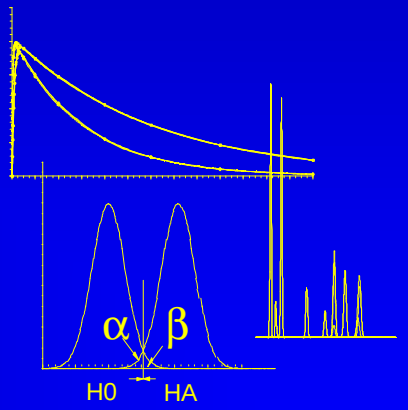
Some topics…

- Design Issues
  - Reference product / batch, dose regimen
  - Fasted / fed state / food effect
  - Standardization
- NCA / PK (PD)
  - Sampling schedule
  - Metrics (AUC, C_{max}; $AUEC$, Ae_{max}, …)
  - One size fits all? ⇒ Unconventional metrics
  - Design, methods, evaluation

Assumptions

World *'Truth'*

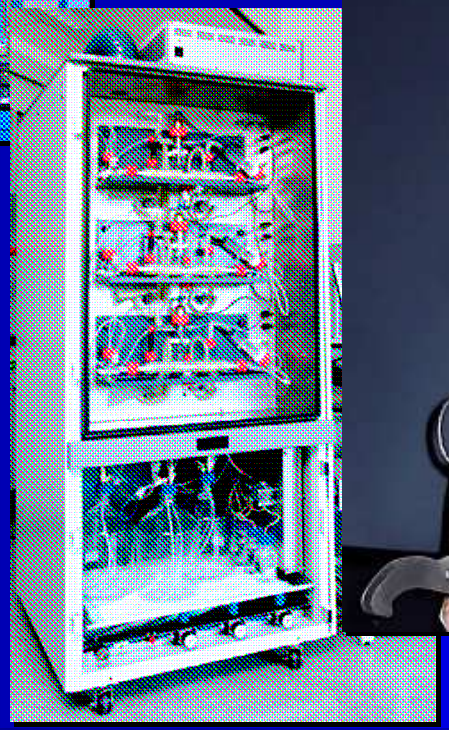


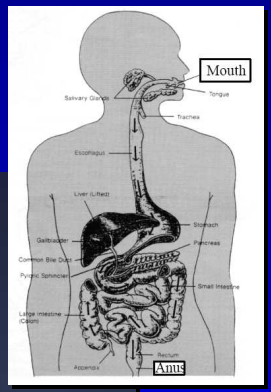


Model *'Data'*

Theory *'Reality'*

Models *vs.* Reality





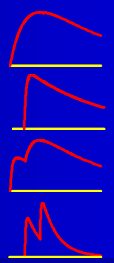
Definition of BE

- EMA GL on BE (2010)

  Two medicinal products containing the same active substance are considered bioequivalent if they are pharmaceutically equivalent or pharmaceutical alternatives and their bioavail-abilities (rate and extent) after administration in the same molar dose lie within acceptable predefined limits. These limits are set to ensure comparable in vivo performance, i.e. similarity in terms of safety and efficacy.

Modified release

- EMA (EUFEPS conference, Barcelona 2011)
  Modified release dosage forms are formulations where the rate and/or site of release of the API(s) is different from that of the conventional (IR) dosage form administered by the same route. This deliberate modification is achieved by special formulation design and/or manufacturing method.
  - Prolonged release
  - Delayed release
  - Biphasic release
  - Pulsatile release



NCA *vs.* PK Modeling

- Noncompartmental methods do not rely on a pharmacokinetic (=compartmental) model
- Also called SHAM (Shape, Height, Area, Moments)
  - Metrics (plasma)
    - Extent of absorption (EU…), total exposure (US): AUC
    - Rate of absorption (EU…), peak exposure (US): C_{max}
    - t_{max} (EU…)
    - Early exposure (US, CAN): $AUC_{t_{max}}$; partial AUC truncated at population (CAN: subject's) t_{max} of the reference
    - Others: C_{min}, Fluctuation, MRT, Occupancy time, t_{lag},…

NCA *vs.* PK Modeling

- Pharmacokinetic models
  - Useful for understanding the drug/formulation
    - Study design of BA/BE!
  - Drawbacks:
    - Almost impossible to validate (fine-tuning of side conditions, weighting schemes, software, …)
    - Still a mixture of art and science.
    - Impossible to recalculate any given dataset using different software – sometimes even different versions of the same software!
    - Not acceptable for evaluation of BA/BE studies!

NCA (Methods)

- Single dose
  - Calculation of Moments of Curve (AUC_t, MRT_t)
    - Linear trapezoidal rule, loglinear trapezoidal rule, or combination (lin-up, log-down).
  - Calculation of half life ($t_{½}$) from elimination rate (λ_z)
    - Unweighted (!) log-linear regression
  - Extrapolation from time point of last quantified concentration to infinity

$$AUC_\infty = AUC_t + \frac{C_t}{\hat{\lambda}_z}$$ or better $$AUC_\infty = AUC_t + \frac{\hat{C}_t}{\hat{\lambda}_z}$$

  - C_{max} / t_{max} directly from profile

NCA (Methods)

- Single dose
  - Method of estimation of λ_z stated in protocol!
    - One-compartment model: TTT-method*
      (Two times t_{max} to t_z)
    - Maximum adjusted R^2 (Phoenix/WinNonlin, Kinetica)

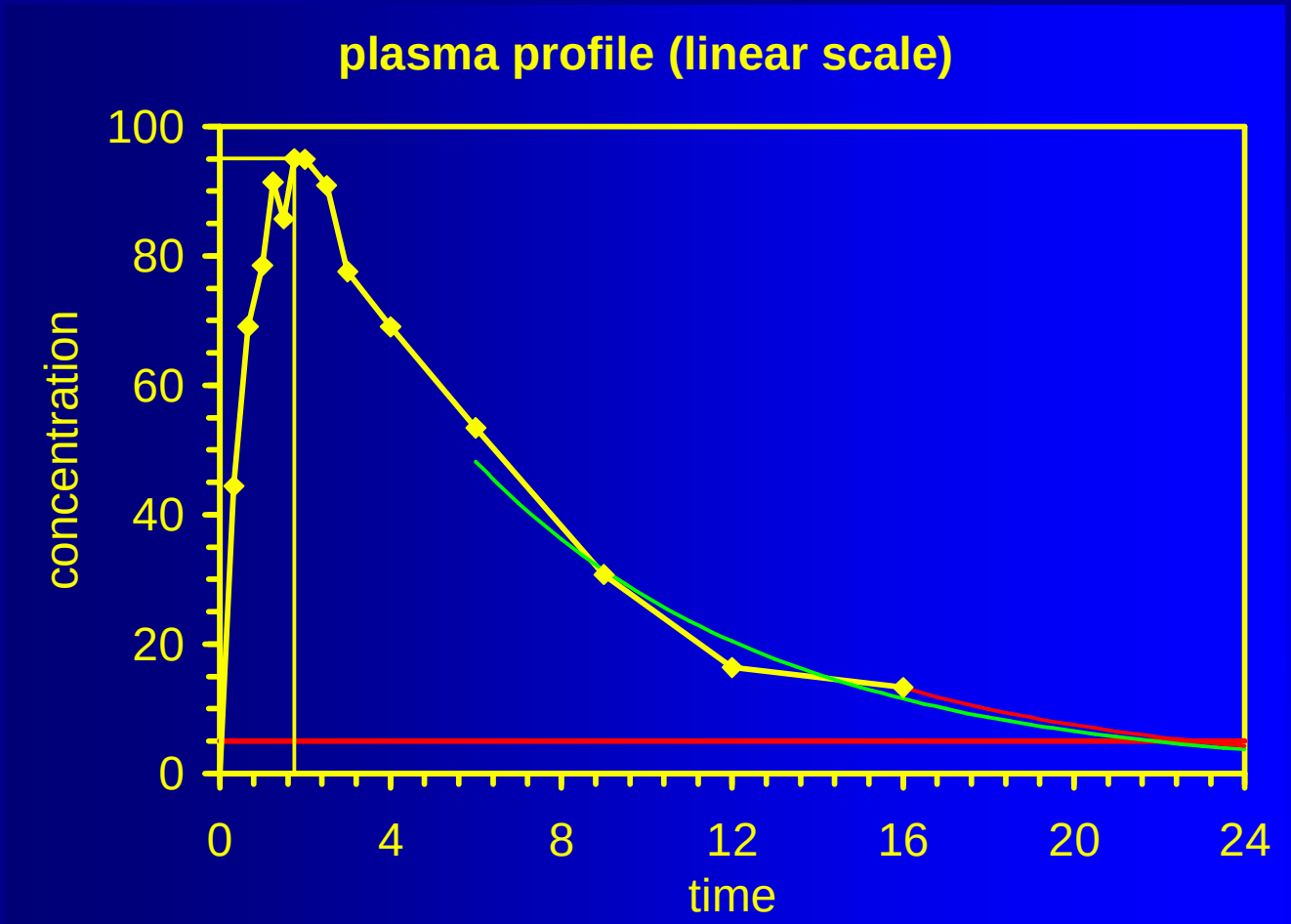
$$R^2_{adj} = 1 - \frac{(1 - R^2) \cdot (n - 1)}{n - 2}$$

WinNonlin ≤5.3: C_{max} **in**cluded
Phoenix/WNL ≥6.0: C_{max} **ex**cluded

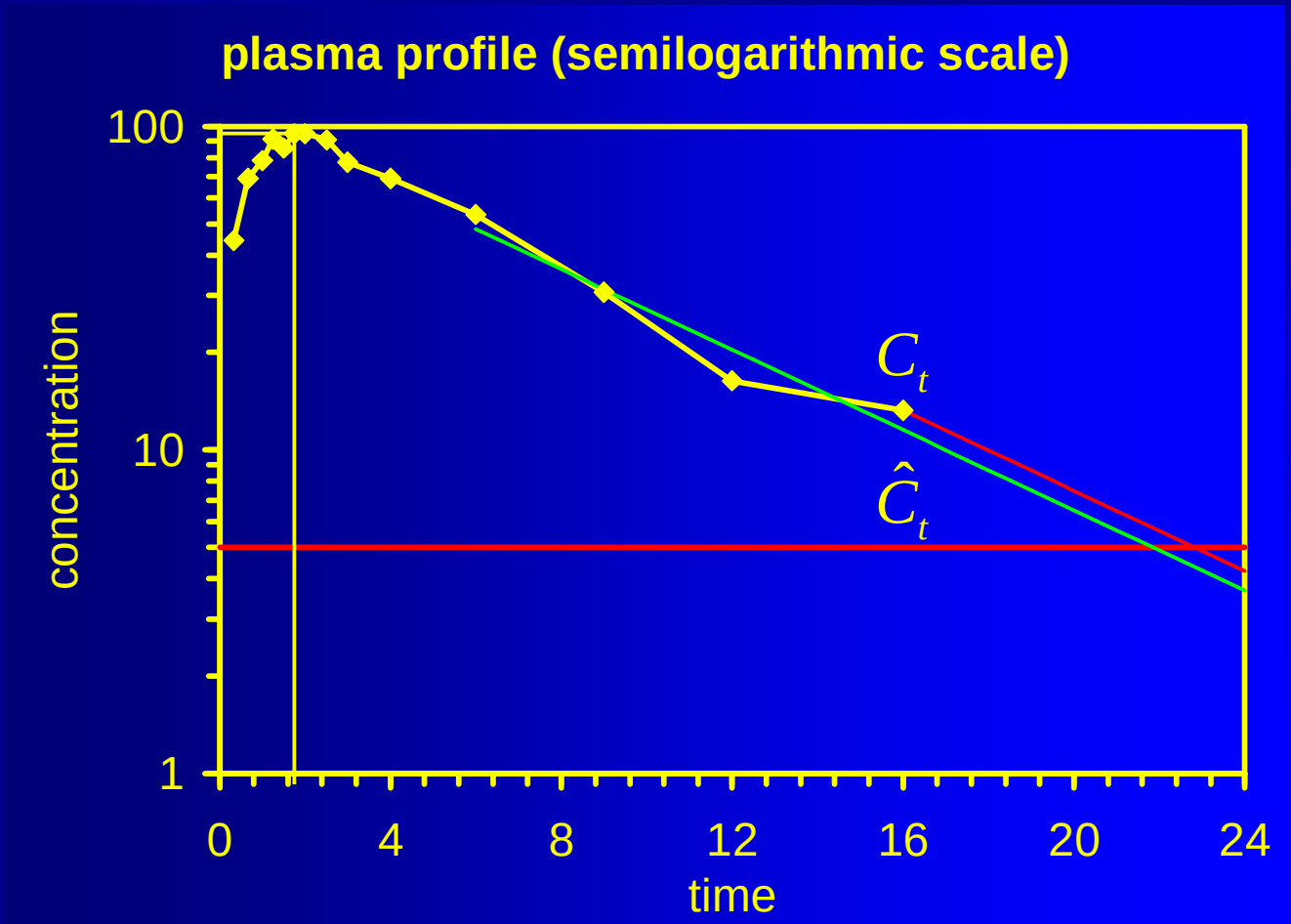
    - Multi-compartment models: starting point = last inflection
    - Minimum AIC $AIC = n \cdot [\ln(2 \cdot \pi) + 1] + n \cdot \ln(RSS/n) + 2 \cdot p$
    - Visual inspection of fit mandatory!

* **Scheerans C, Derendorf H and C Kloft**
Proposal for a Standardised Identification of the Mono-Exponential Terminal Phase for Orally Administered Drugs
Biopharm Drug Dispos 29, 145–157 (2008)

NCA (Methods)


plasma profile (linear scale)
concentration
100
80
60
40
20
0
0
4
8
12
16
20
24
time

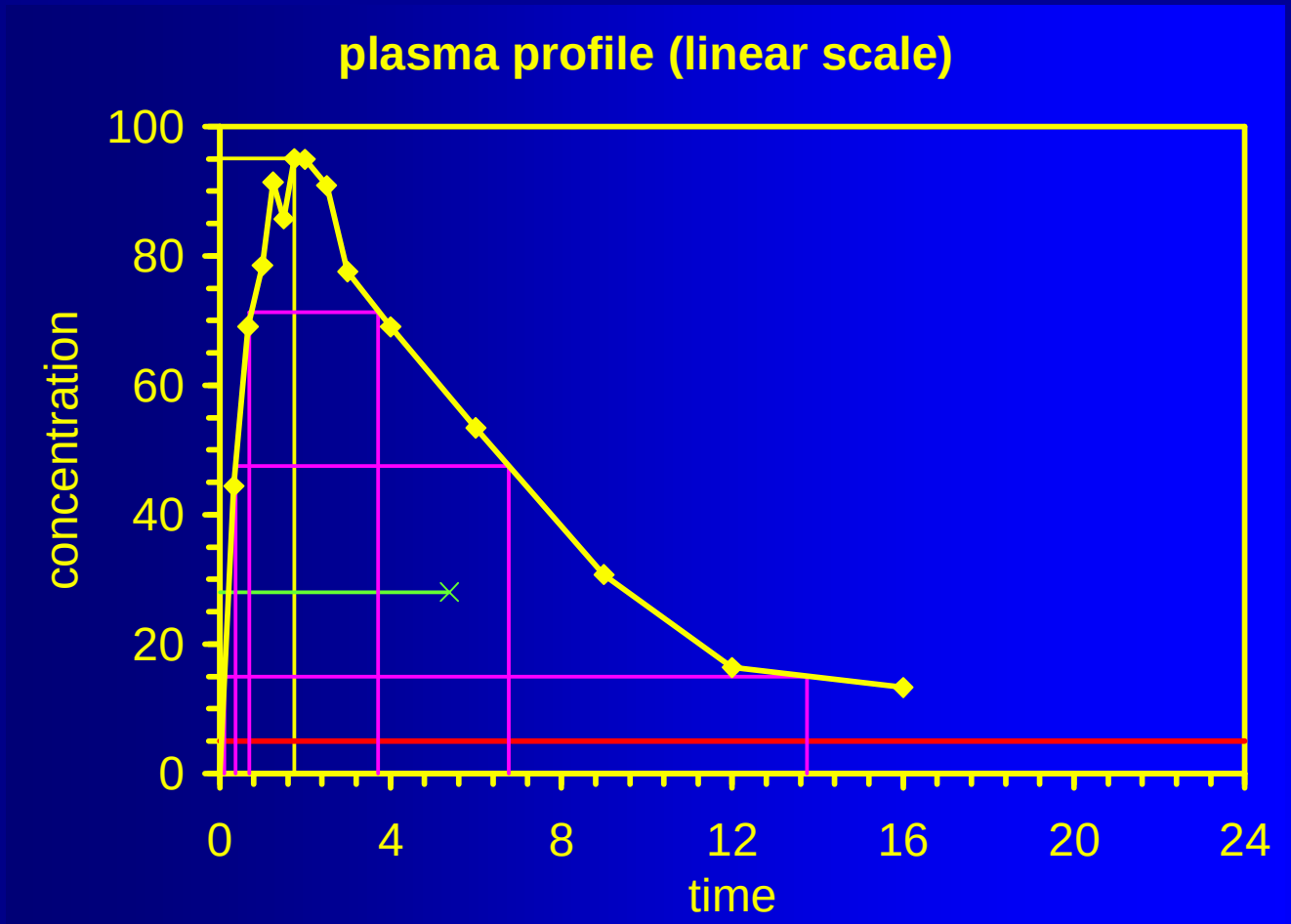
NCA (Methods)


plasma profile (semilogarithmic scale)
100
10
1
concentration
C_t
$\hat{C}_t$
0
4
8
12
16
20
24
time

NCA (Methods)

- Single dose
  - Unconventional parameters describing the shape of profiles
    - C_{max}/AUC
    - $t_{75\%}$ or $POT\text{-}25$ (Plateau Time: interval where $C(t) \geq 75\%$ of C_{max} aka Peak Occupancy Time 25: time interval where $C(t)$ is within 25% of C_{max})
    - HVD or $POT\text{-}50$ (Half Value Duration, Peak Occupancy Time 50: time interval where $C(t) \geq 50\%$ of C_{max})
    - Occupancy time, $t \geq MIC$ (time interval where $C(t)$ is above some limiting concentration)

NCA (Methods)


plasma profile (linear scale)
concentration
100
80
60
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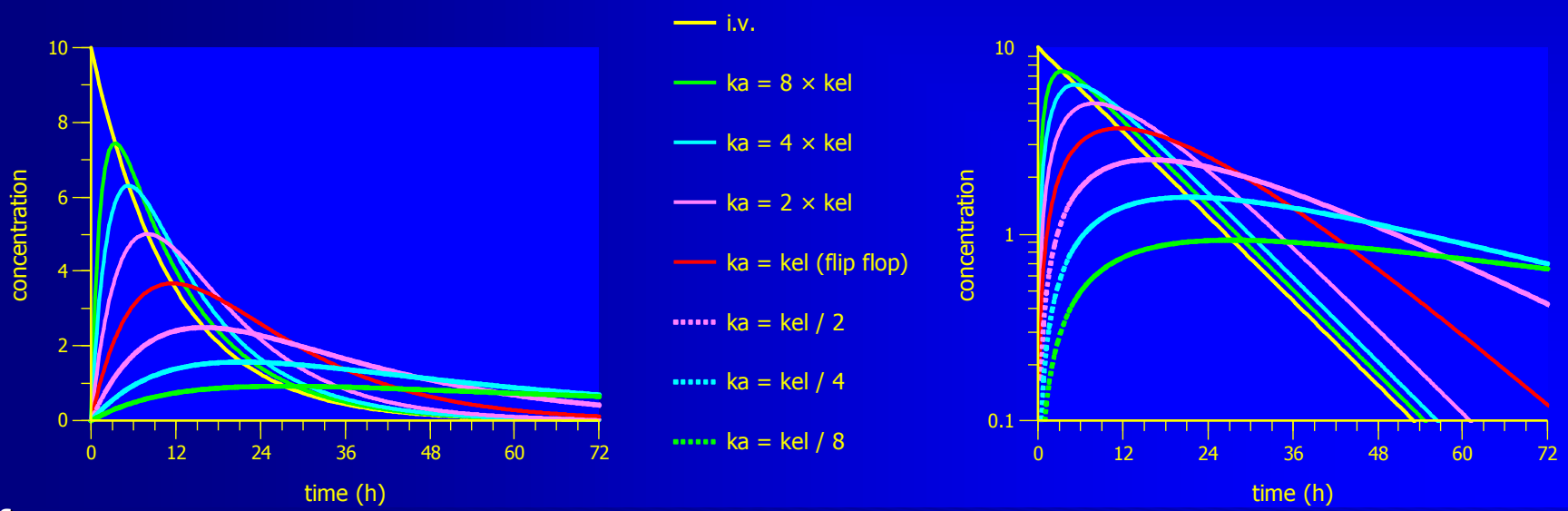
24
time

Excursion into PK

- AUC_{72} vs. AUC_{∞}
  - Bioequivalence assesses similarity of absorption (product specific) – not elimination (drug specific)
  - Most suitable metric if $k_a < k_{el}$?



Excursion into PK

- AUC_{72} vs. AUC_{∞}

  V 10, D 100, F 100%, k_{el} 0.08664 ($t_{½,el}$ 8 h), k_a 0.6931 h^{-1} – 0.01083 h^{-1} ($t_{½,a}$ 1 h – 64 h), $AUC_{0-\infty}$ 115.42

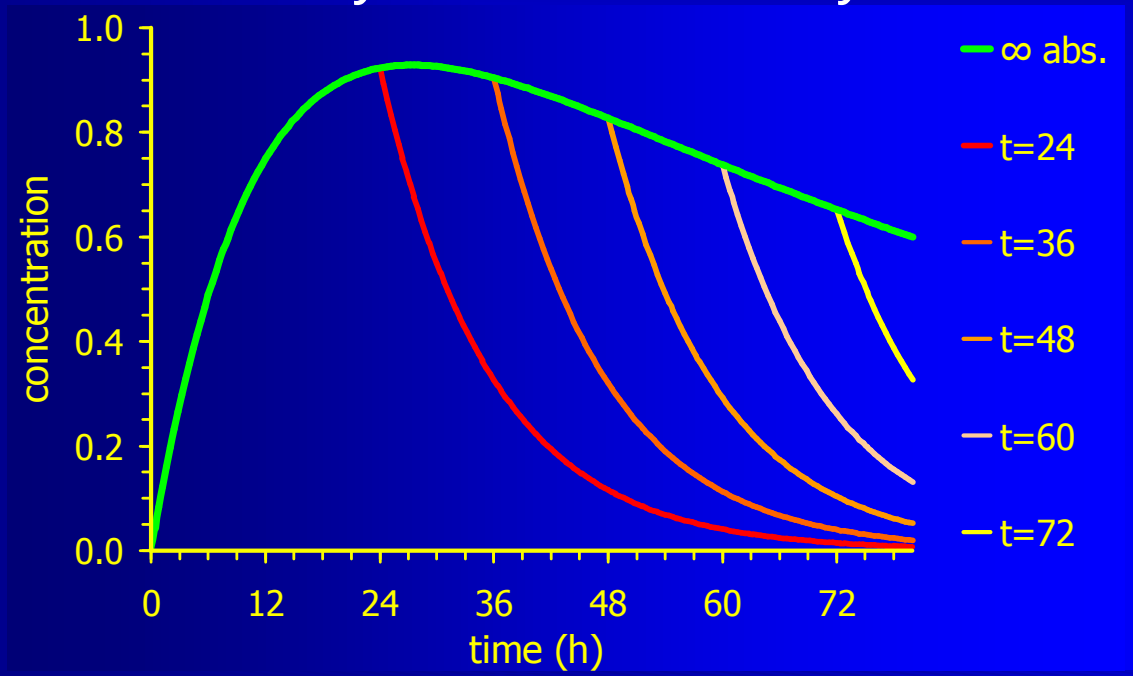
PK	λ_z	$t_{½}$	AUC_{0-72}	$AUC_{0-\infty}$	% extr.	Bias (%)
i.v.	0.08664	8.0000	115.19	115.42	0.20	<0.0001
$k_a = 8 \times k_{el}$	0.08608	8.0527	115.10	115.41	0.27	-0.0067
$k_a = 4 \times k_{el}$	0.08608	8.0527	115.10	115.41	0.27	-0.0067
$k_a = 2 \times k_{el}$	0.08493	8.1611	114.96	115.42	0.40	+0.0079
$k_a = k_{el}$ (flip flop)	0.07040	9.8459	113.78	115.53	1.51	+0.0953
$k_a = k_{el} / 2$	0.04011	17.282	105.43	116.01	9.12	+0.5143
$k_a = k_{el} / 4$	0.02046	33.871	83.14	117.13	29.20	+1.4866
$k_a = k_{el} / 8$	0.01021	67.892	54.97	118.91	53.77	+3.0247

Excursion into PK

- AUC_{72} *vs.* AUC_{∞}
  - Is it always justified to use AUC_{72} (truncated AUC) as the primary PK metric for extent of absorption?
  - No problems for IR formulations ($k_a \gg k_{el}$), since absorption completed after $2–4\times t_{max}$
  - Controlled release may call for a different strategy
  - Going beyond flip flop PK ($k_a = k_{el}$) the *measured* AUC will mainly reflect elimination (drug specific); we don't *'see'* the absorption phase (formulation specific)
  - Little bias (+3%) even for $k_a = 8\times k_{el}$ if AUC_{∞} is used

Excursion into PK

- AUC_{72} vs. AUC_{∞}
  - Cave! Absorption is completed if the formulation leaves the body – elimination only…



NCA (Methods)

- Multiple dose
  - Calculation of AUC_{τ} (dosage interval τ); $AUC_{ss,24h}$ if more than *o.a.d.* and chronopharmaco-logical variation)
  - $C_{ss,max}$ directly from profile
  - $C_{ss,min}$ from profile *or* better if missing values / time deviations $\hat{C}_{ss,min} = C_z e^{-\hat{\lambda}_z(\tau - t_z)}$
  - Peak-Trough-Fluctuation $(C_{ss,max} - C_{ss,min}) / C_{ss,av}$, where $C_{ss,av} = AUC_{\tau} / \tau$
  - Swing $(C_{ss,max} - C_{ss,min}) / C_{ss,min}$
  - AUCF AUC above $C_{ss,av}$ / AUC_{τ}

NCA (alternative metrics)

- Comparison of the shape of profiles
  - f_1 'Difference factor'; borrowed from dissolution testing
    - f_1 proportional to the average difference between the two profiles

$$f_1 = 100 \cdot \frac{\sum_{t=1}^{t=n} \left| C_{R,t_i} - C_{T,t_i} \right|}{\sum_{t=1}^{t=n} C_{R,t_i}}$$

    - Suggested cut-off: Bioequivalent if $f_1 \leq 20$

* JW Moore and HH Flanner
Mathematical Comparison of curves with an emphasis on in vitro dissolution profiles
Pharm Tech 20/6, 64–74 (1996)

NCA (alternative metrics)

- Comparison of the shape of profiles
  - Problems with f_1
    - Not a statistic!
    - Value dependent on the location and number of sampling time points
    - Uses differences (rather than ratios) of concentrations (additive instead of multiplicative model)
    - Arbitrary cut-off (≤ 20) suitable?

NCA (alternative metrics)

- Comparison of the shape of profiles
  - ξ_i 'Bioequivalence index'*

$$\xi_i = \left(\frac{\int_0^\infty |C_R(t) - C_T(t)|^i}{\int_0^\infty |C_R(t) + C_T(t)|^i} \right)^{\frac{1}{i}} \quad i \in \mathbb{N}^+ \qquad 0 \le \xi_i \le 1$$

  - ξ_i = 0 if profiles are identical
  - ξ_i = 1 if one of the profiles shows only 'zero' values

* A Rescigno
Bioequivalence
Pharm Res 9, 925–8 (1992)

NCA (alternative metrics)

- Comparison of the shape of profiles
  - ξ_i 'Bioequivalence index'
    - Selection of i arbitrary (1 – 3 tried in literature)
    - Approximation of $\int_0^\infty$ by trapezoidal rule correct?
    - Not a statistic
    - Suggested cut-off: Bioequivalent if median $\xi_i \leq 0.1$
    - Generally $\xi_1 < \xi_2 < \xi_3$; meaning?

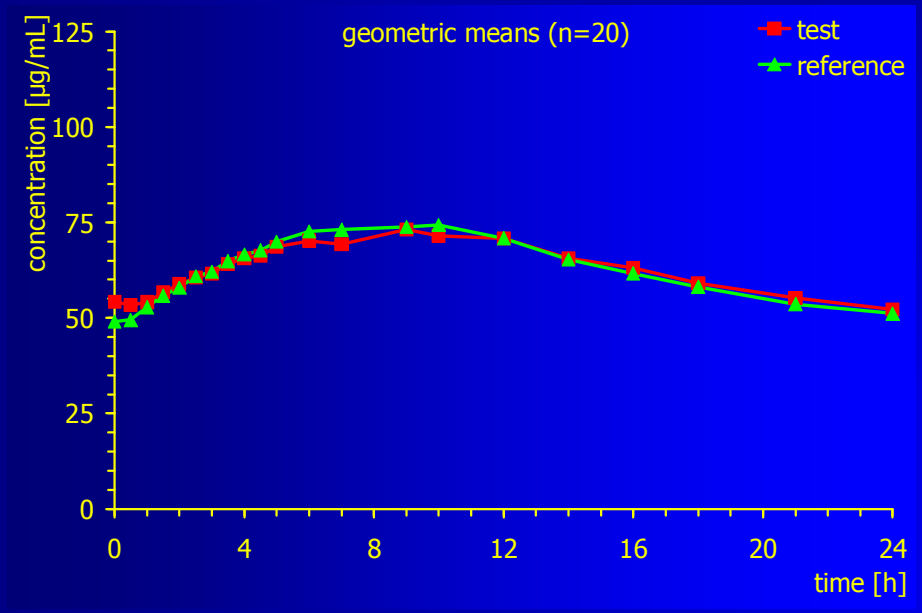
NCA (alternative metrics)

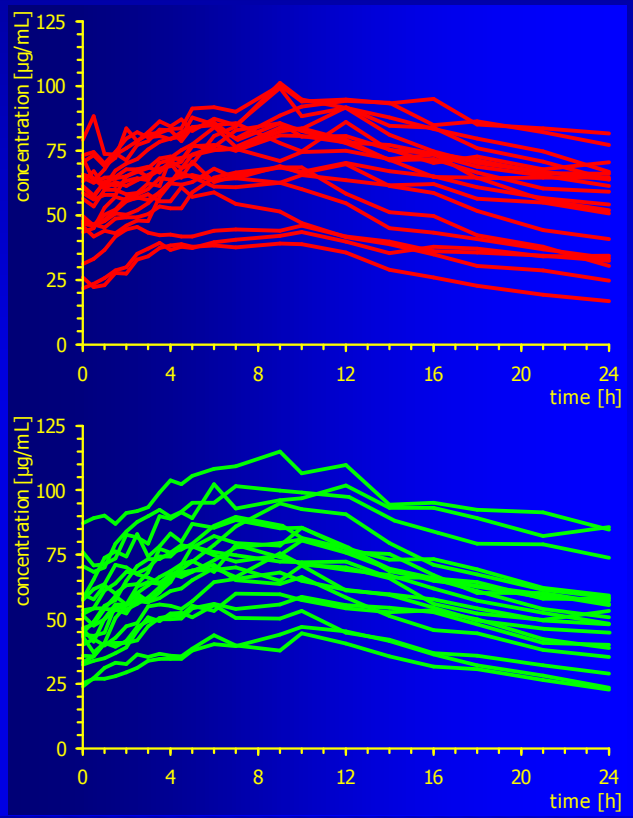
- Comparison of the shape of profiles
  - Many more (or less esoteric) metrics suggested
    - Chinchilli metric ψ
    - Polli and McLean metrics (ρ, ρ_m, δ_a, δ_s)
    - Karalis and Macheras metrics ($MARD$, $MARD_{w1}$, $MARD_{w2}$)
    - Percentage of the Common Area (PCA)
    - Problems common with all profile metrics: identical time points assumed (time deviations, missing values?)
    - No clear benefits; more research needed
    - For an overview see

HA Bayoud and AM Awad
Performance of Several Bioequivalence Metrics for Assessing the Rate and Extent of Absorption
J Bioequiv Availab 3/7, 174–7 (2011)
doi: 10.4172/jbb.1000080

NCA (alternative metrics)

- MR valproic acid 500 mg o.a.d. fasting (n=20)





NCA (alternative metrics)

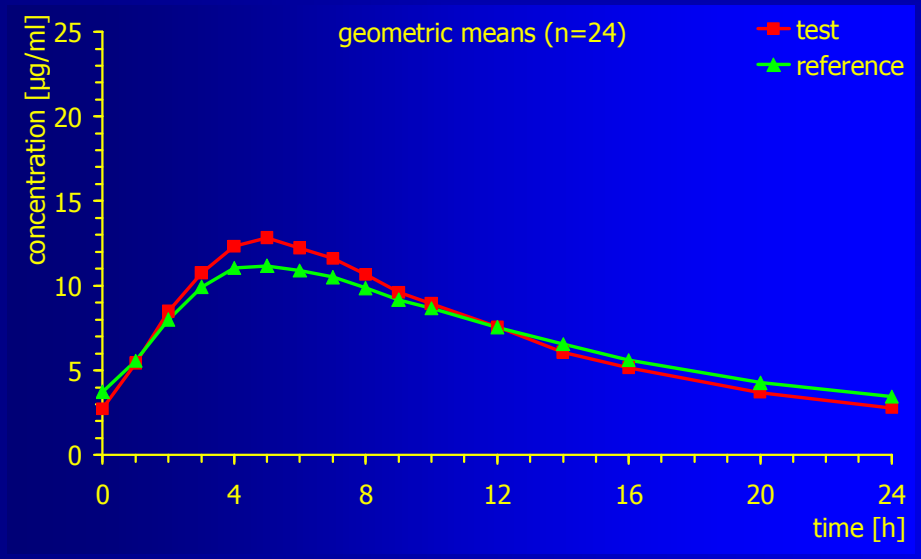
- MR valproic acid 500 mg o.a.d. fasting (n=20)

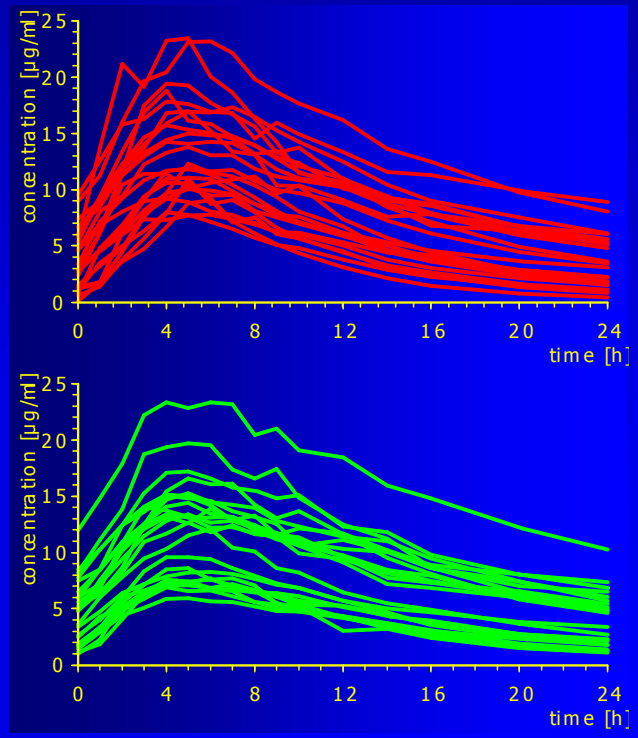
metric	90% CI	
AUC_τ	95.6%	105.9%
C_{max}	94.0%	102.3%
C_{min}	94.1%	109.3%
MRT_τ	98.6%	101.7%
$\%PTF$	76.4%	106.1%
$Swing$	67.9%	104.3%
$pAUC$	87.7%	122.3%
$FAUC$	73.0%	100.5%

metric	median	BE criterion
f_1	11.38	≤20
ξ_1	0.05535	≤0.1
ξ_2	0.06227	≤0.1
ξ_3	0.06660	≤0.1
ψ	0.7433	≤1
ρ	1.120	≤1.4
ρ_m	0.1196	≤0.35
δ_a	0.1086	≤0.27
δ_s	0.01906	≤0.102
$MARD$	0.1218	≤0.2
$MARD_{w1}$	0.1187	≤0.2
$MARD_{w2}$	0.1668	≤0.2
PCA	0.8951	≥0.82

NCA (alternative metrics)

- MR theophylline 400 mg o.a.d. fasting (n=24)





NCA (alternative metrics)

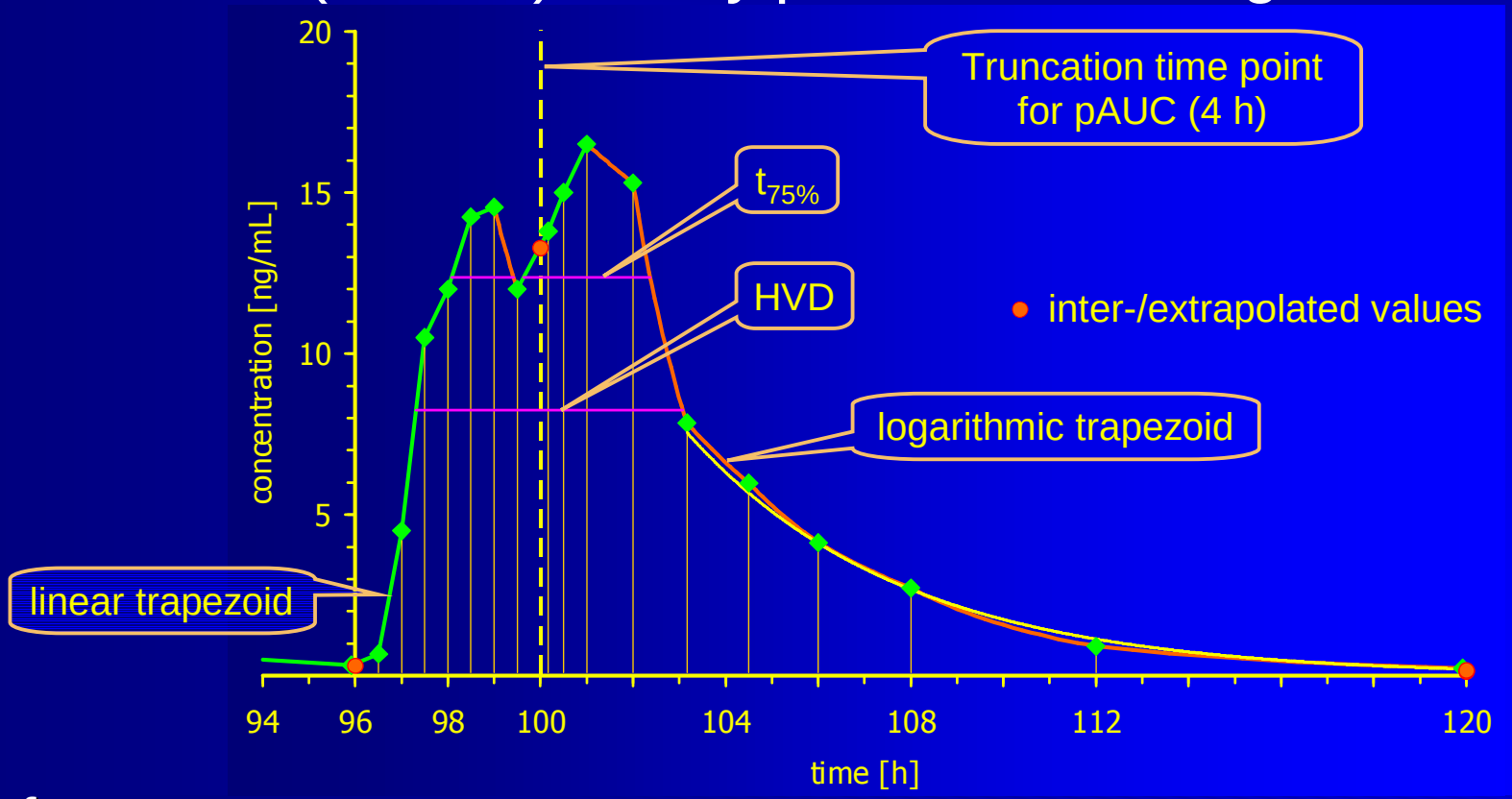
- MR theophylline 400 mg o.a.d. fasting (n=24)

metric	90% CI	
AUC_τ	96.6%	108.3%
C_{max}	107.9%	123.9
C_{min}	56.2%	92.6%
MRT_τ	93.2%	97.0%
$\%PTF$	116.9%	132.8%
$Swing$	136.4%	228.9%
$FAUC$	114.5%	129.6%

metric	median	BE criterion
f_1	17.53	≤20
ξ_1	0.08352	≤0.1
ξ_2	0.09176	≤0.1
ξ_3	0.09988	≤0.1
ψ	1.014	≤1
ρ	1.193	≤1.4
ρ_m	0.1934	≤0.35
δ_a	0.1086	≤0.27
δ_s	0.3360	≤0.102
$MARD$	0.1920	≤0.2
$MARD_{w1}$	0.1793	≤0.2
$MARD_{w2}$	0.2891	≤0.2
PCA	0.8422	≥0.82

NCA (alternative metrics)

- MR (IR+DR) methylphenidate 60 mg o.a.d. fed



NCA (problems)

- C_{min}
  - Defined by EMA as the concentration (C_{trough}) at the *end* of the dosing interval τ
  - Cave: Not implemented in PK software (Phoenix/ WinNonlin, Kinetica: C_{min} = minimum concentration within τ). Requires adaption.
  - As a single point metric even more variable than C_{max} (close to LLOQ if little accumulation).
  - EMA requires pre-dose sampling at ≤–5 min and sampling at τ ±10 min
  - In a switch-over o.a.d. last sample 23:55 in P1 and at 24:00 in P2

NCA (problems)

- C_{min}
  - Missing last samples may lead to *'Apples-and-Oranges' statistics* (biased treatment effect)
  - If a reliable estimate of λ_z is possible (≥3 data points), we can use the estimate
    - ± shift of C_z according to λ_z*

$$\hat{C}_{ss,min} = C_z e^{-\hat{\lambda}_z(\tau - t_z)} \quad (1)$$

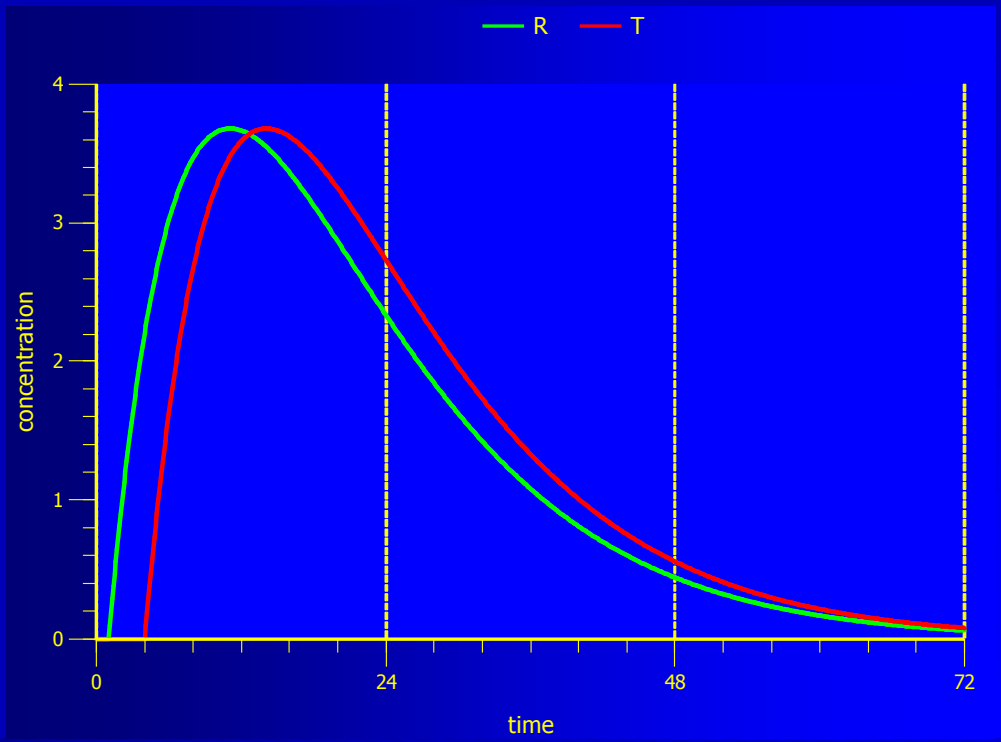
    - Estimation independent from measured C_z

$$\hat{C}_{ss,min} = e^{\left(\hat{C}_0 - \hat{\lambda}_z \cdot (t_0 + \tau)\right)} \quad (2)$$

* Gabrielsson J and D Weiner
Pharmacokinetic & Pharmacodynamic Data Analysis: Concepts and Applications
Swedish Pharmaceutical Press, Stockholm, p163 (4th ed. 2006)

NCA (problems)

- C_{min}
  - DR, flip flop PK; V 10, D 100, F 100%, k 0.09902 h^{-1} ($t_{½}$ 7 h), $t_{lag,R}$ 1 h, $t_{lag,T}$ 4 h, C_{max} 3.68, $AUC_{0-\infty}$ 101.0



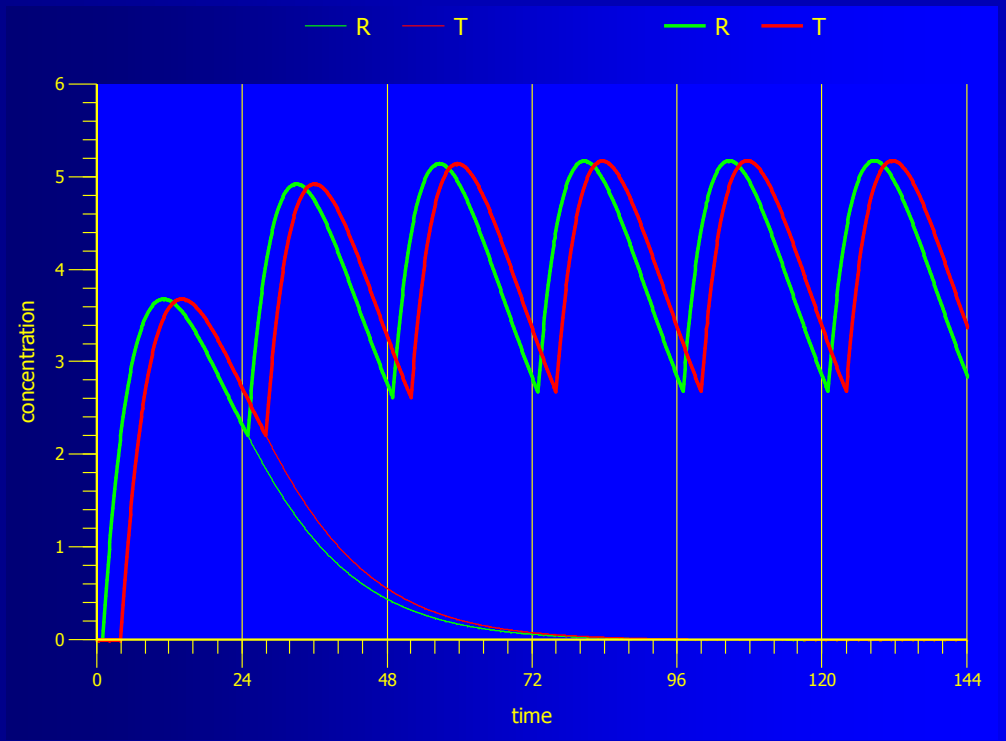
NCA (problems)

- C_{min}
  - Can we make a prediction about similarity of formulations in steady state from SD data (thus avoiding the required MD study)?
  - Concentration at the intended dosage interval (here C_{24}) in discussion (EUFEPS Barcelona 02/11 ✓, informa Berlin 11/11 ✗)

Metric	T	R	T / R	T – R
t_{lag}	4.00	1.00	NA	+3.00
AUC_{0-24}	59.45	67.05	0.8867	NA
AUC_{0-72}	100.08	100.27	0.9979	NA
$AUC_{0-\infty}$	101.05	101.03	1.0002	NA
C_{24}	2.7332	2.3354	1.1703	NA
C_{72}	0.0802	0.0622	1.2890	NA

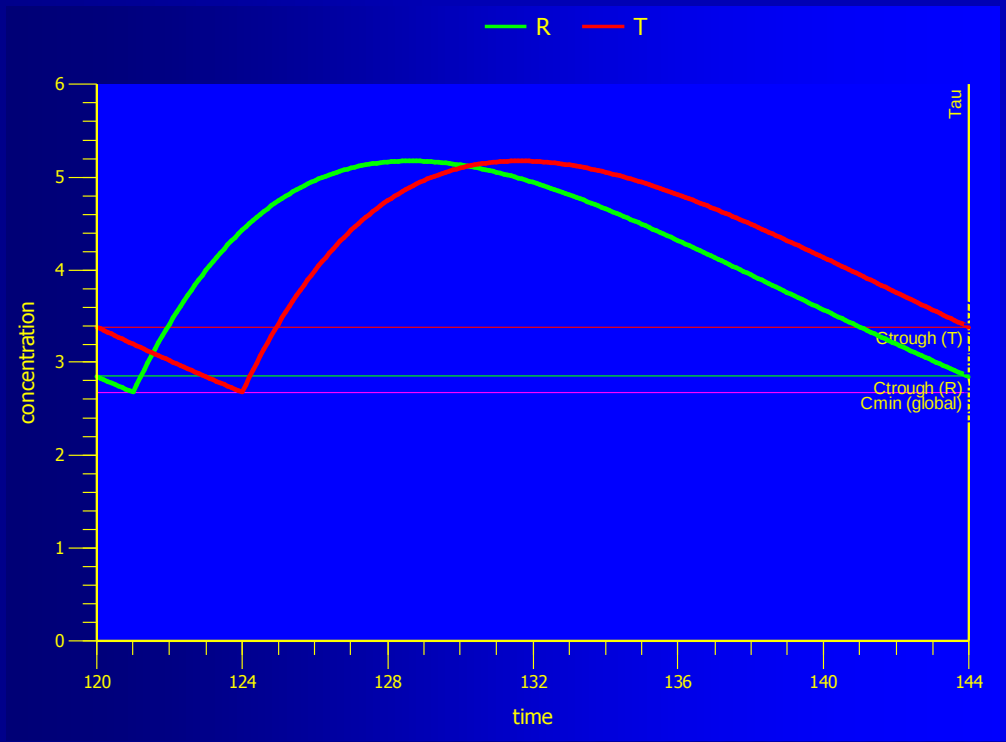
NCA (problems)

- C_{min}
  - Simulation of steady state (τ 24 h; 6 d ≈ 20×$t_{½}$)



NCA (problems)

- C_{min}
  - *'Which'* C_{min} reflects difference in formulations?



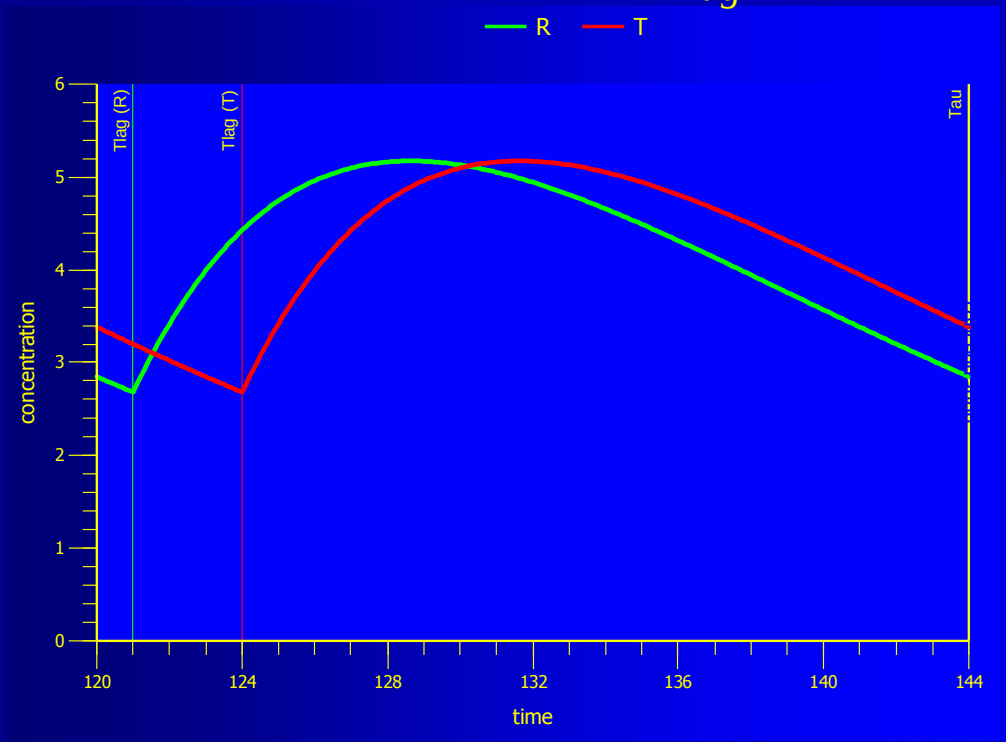
- Global C_{min} is identical (2.682)!
- C_{trough} is discriminatory:

T	3.383
R	2.850
T/R	118.73%

- BTW: AUC_{τ} and C_{max} identical (linear PK)

NCA (problems)

- Only C_{min}?
  - But formulations differ in t_{lag}! Why use a surrogate?



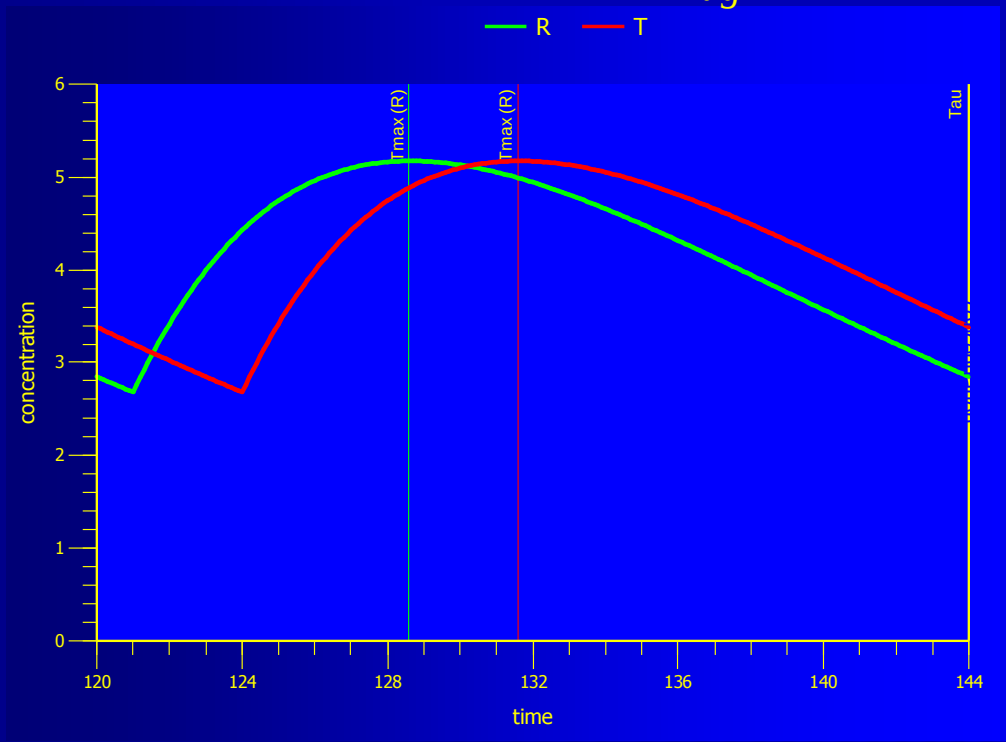
- t_{lag} is discriminatory:

T	4
R	1
T – R	+3

- Might be difficult to measure; frequent sampling required
- Nonparametric statistics (EMA!)

NCA (problems)

- Only C_{min}?
  - But formulations differ in t_{lag}! Why use a surrogate?



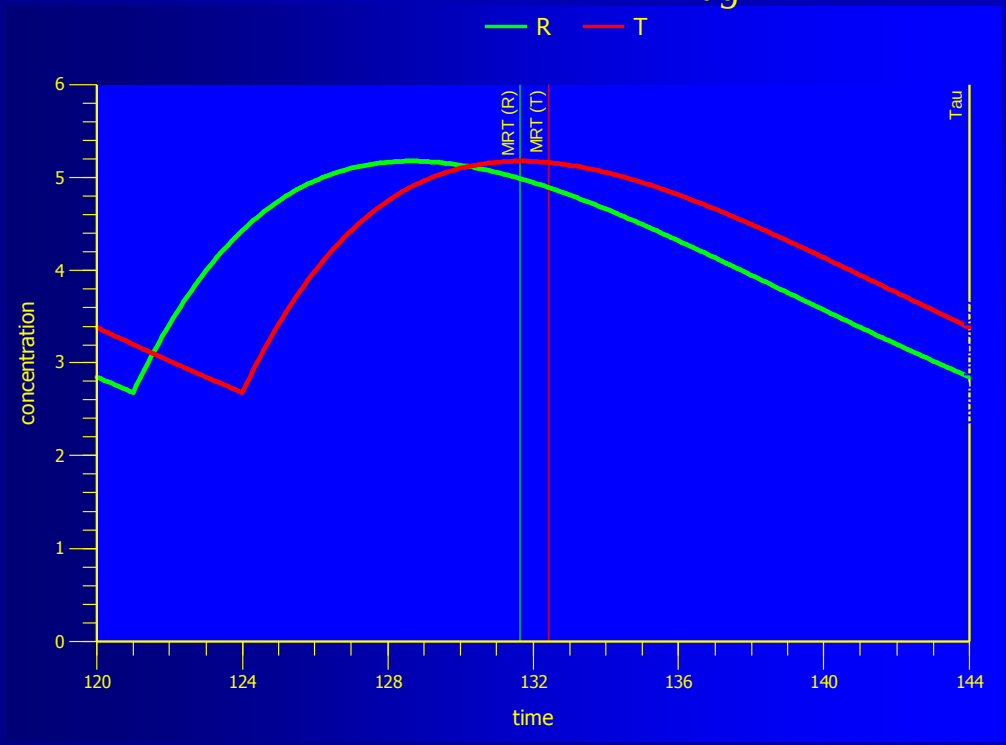
- t_{max} is discriminatory as well:

T	14.1
R	11.1
T – R	+3

- Maybe better; frequent sampling in the area of C_{max} usual
- Nonparametric statistics (EMA!)

NCA (problems)

- Only C_{min}?
  - But formulations differ in t_{lag}! Why use a surrogate?



- C_{trough}, t_{lag}, and t_{max} are single point metrics; high variability!
- MRT uses the information of the entire profile; discriminatory?

T	12.43
R	11.64
T – R	+0.78

NCA (problems)

- EU GL 2010 (Section 4.1.8)
  - A statistical evaluation of t_{max} is not required. However, if rapid release is claimed to be clinically relevant and of importance for onset of action or is related to adverse events, there should be no apparent difference in median t_{max} and its variability between test and reference product.

What's this?

How to assess that?
'A non-parametric analysis is not acceptable.'

NCA (problems)

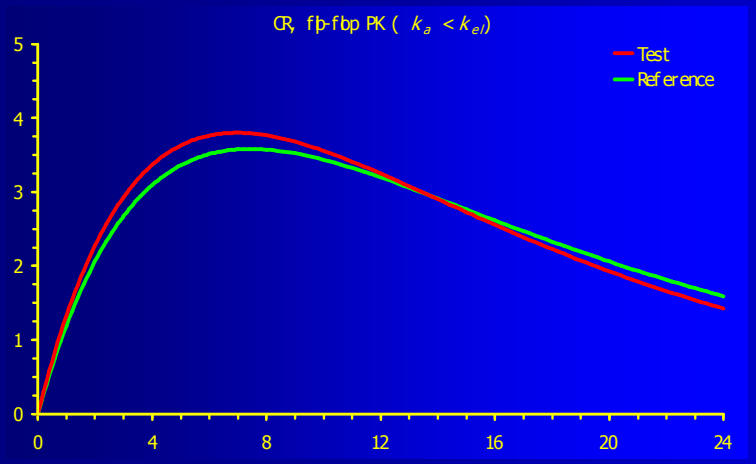
- PK metrics which are not continous, but sampled from a discrete distribution (t_{max}, t_{lag}) *must* (!) be evaluated by a nonparametric method
  - Especially for delayed release formulations it is hypocritical to require a surrogate (C_{min}) – instead assessing the metric *causing* the formulations' difference (t_{lag})
  - It's high time for EMA to reconsider their idiosyncrasies towards well-established statistical methods

NCA (problems)

- Can we make a prediction about similarity of formulations in steady state from SD data (avoiding the MD study)?
  - Concentration at the intended dosage interval (*e.g.*, C_{24}) in discussion (EUFEPS Barcelona 2011)
  - C_z is dependend on all formulation-specific PK parameters (F, k_a, t_{lag})
  - No direct correlation between C_z and accumulation ratio
  - Accumulation depends *only* on the amount of drug remaining in the body at the next administration (expressed as $AUC_{0-\infty} - AUC_{0-t}$)

NCA (problems)

- CR formulation, flip flop PK, D 100, V 5, F_R 100%, F_T 95%, k_{el} 0.231 h^{-1} ($t_{½}$ 3 h), $k_{a,R}$ 0.0693 h^{-1} ($t_{½}$ 10 h), $k_{a,T}$ 0.0815 h^{-1} ($t_{½}$ 8.5 h)

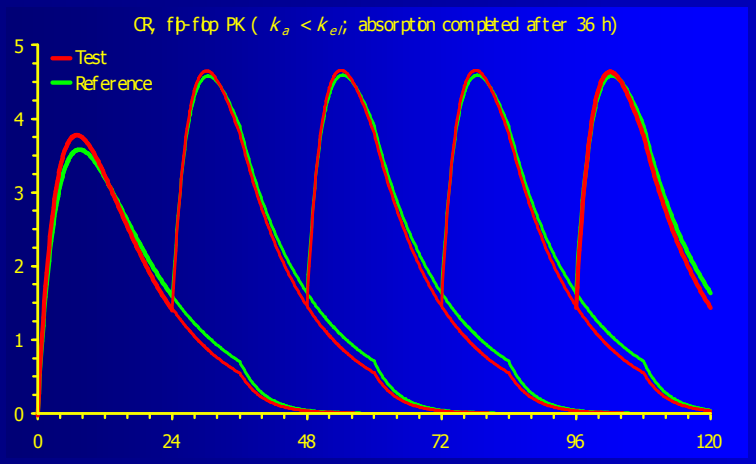


Metric	T	R	T / R	80 –125%
C_{max}	3.800	3.581	106.1%	pass
$AUC_{0–24}$	64.45	63.27	101.9%	pass
$AUC_{0–\infty}$	82.88	87.43	94.8%	pass
$AUC_{24–\infty}$	18.43	24.15	76.3%	fail
extrapol.	22.2%	27.6%	NA	NA
C_z	1.424	1.590	89.5%	pass

- Common metrics (and C_z) pass – but will Test accumulate less than Reference and fail in steady state (predicted by $AUC_{24–\infty}$)?

NCA (problems)

- CR formulation, flip flop PK, absorption completed after 36 hours)

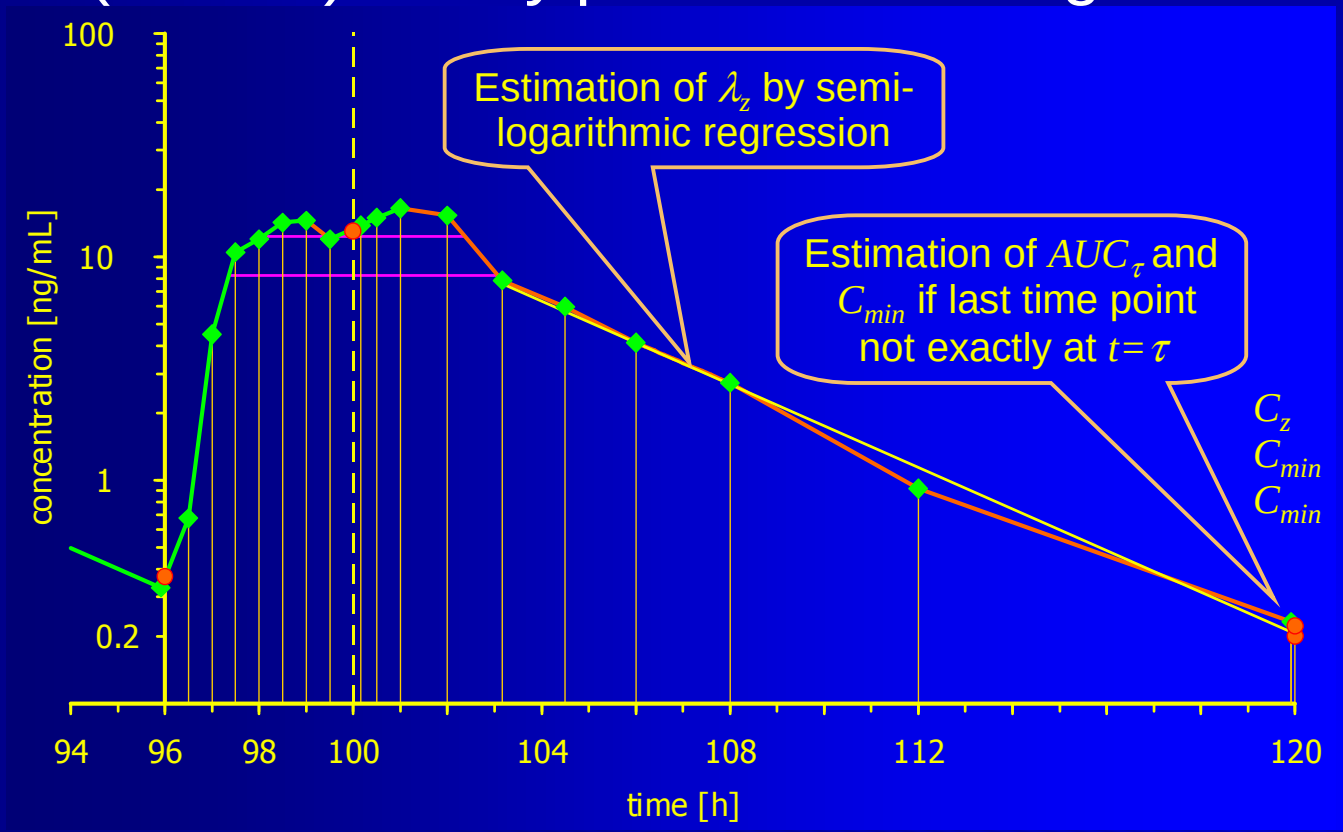


Metric	T	R	T / R	80 –125%
C_{max}	4.659	4.591	101.5%	pass
$AUC_{0-\tau}$	77.86	79.42	98.0%	pass

- Common metrics pass; C_{max} is less sensitive to detect differences in steady state (101.5%) than after a single dose (106.1%)
- Know your formulation!
- Prediction based on C_z removed from MR draft (Berlin 11/2011)

NCA (example)

- MR (IR+DR) methylphenidate 60 mg o.a.d. fed



NCA (example)

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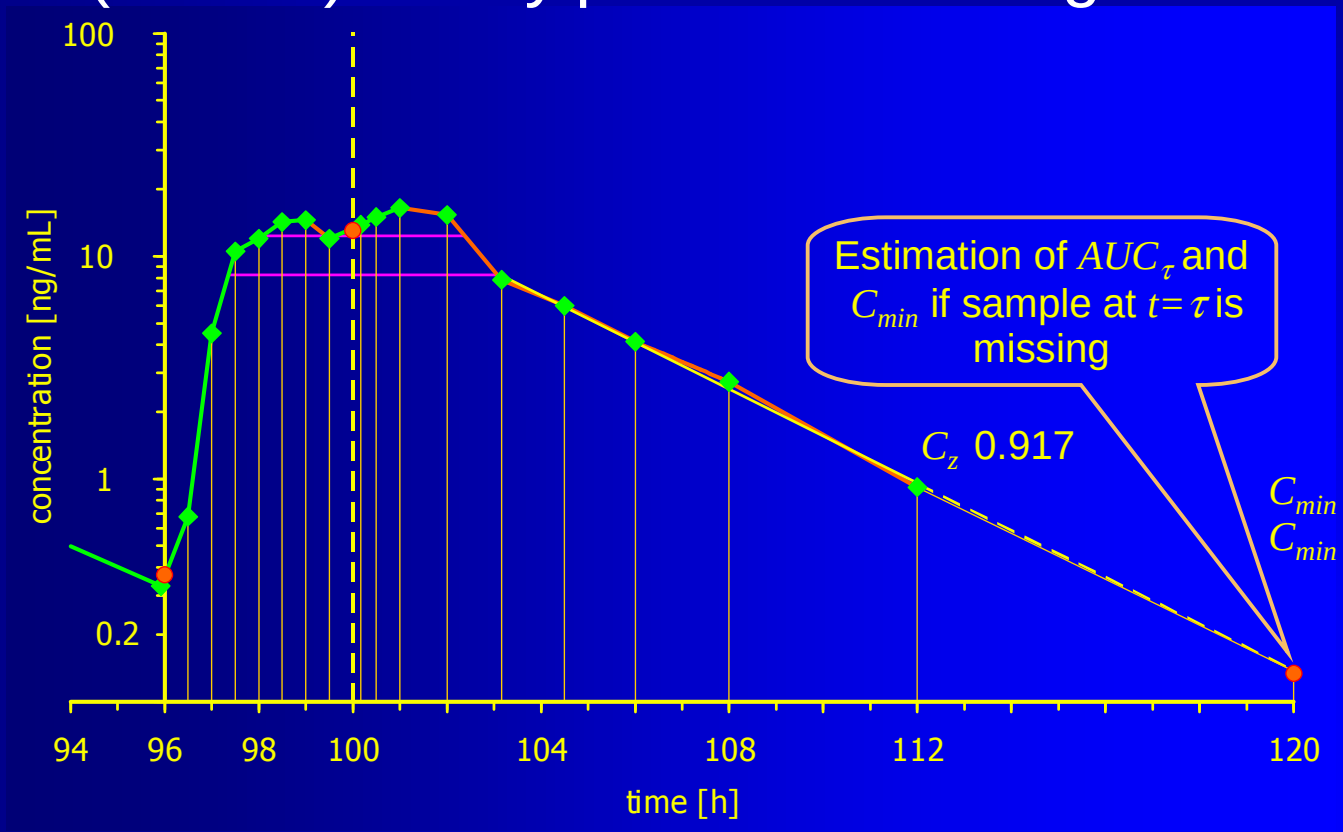

NCA (example)

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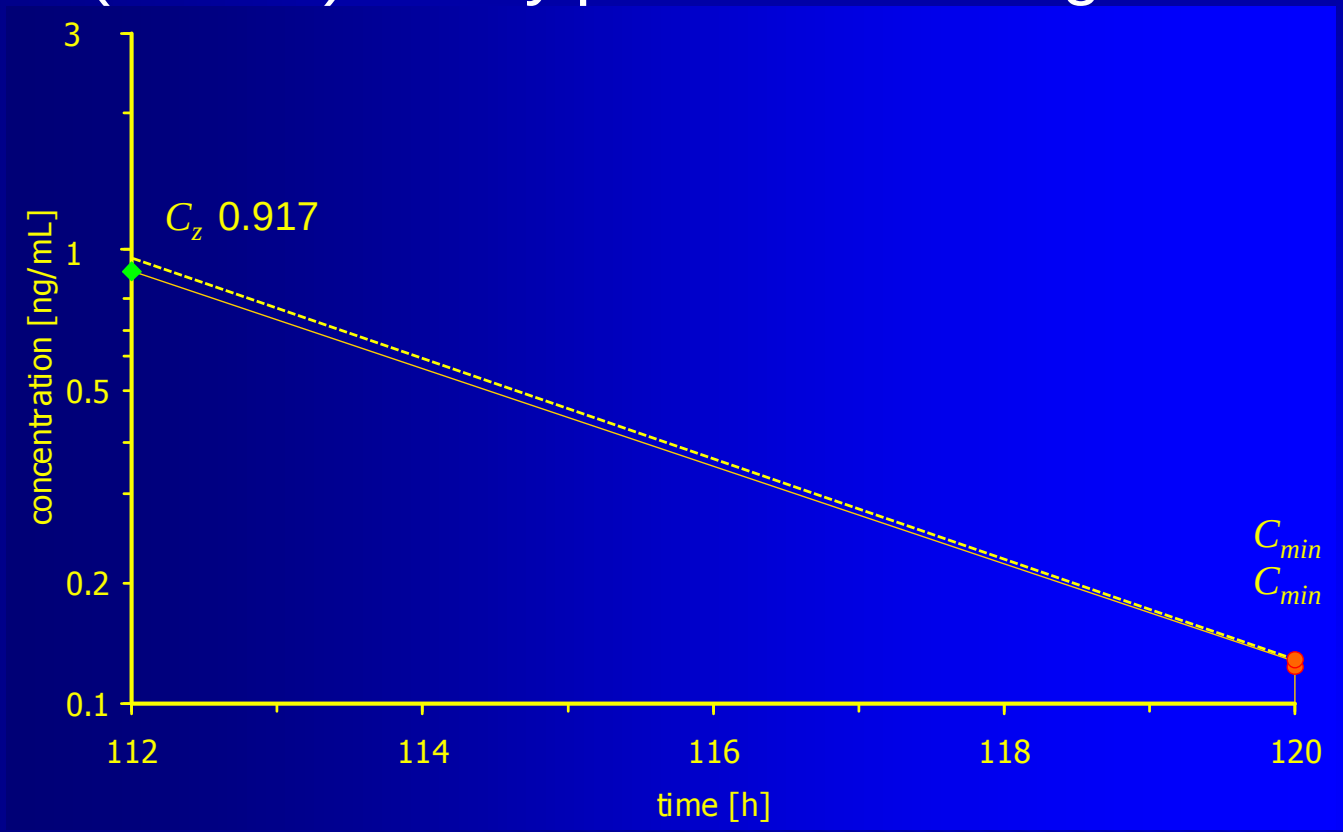
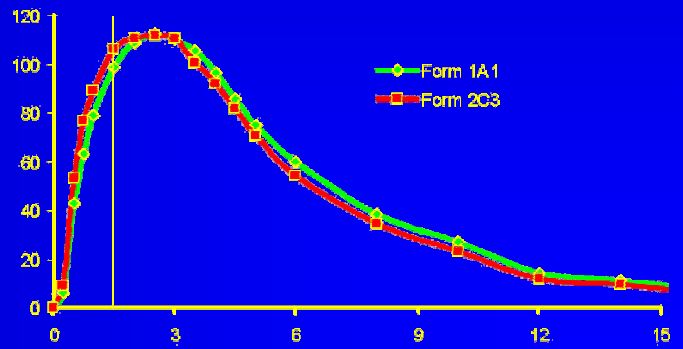


NCA (alternative metrics)

- Partial *AUC* (*pAUC*) for multiphasic profiles
  - Truncated *AUC* (at a time point based on clinical considerations)
  - First *pAUC* describes early onset, second *pAUC* maintenance of levels
    - Examples: Zolpidem ER, Methylphenidate SR/ER
    - First guidance on Zolpidem issued in 2009

$AUC_{0-1.5}$ (~ sleep onset)
$AUC_{1.5-t}$ (~ sleep maintenance)
$AUC_{0-\infty}$, C_{max}



FDA (Office of Generic Drugs, CDER)
Draft Guidance on Zolpidem
August 2009
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM175029.pdf

NCA (alternative metrics)

- *pAUC* for multiphasic profiles
  - ER Zolpidem: $AUC_{0-1.5}$ *may* be highly variable; scaling? (not acceptable for EMA!)

N	parameter	C_{max}	$AUC_{0-1.5}$	$AUC_{1.5-t}$	$AUC_{1.5-\infty}$	$AUC_{0-\infty}$
72	PE (90% CI)	1.02 (0.96 – 1.10)	1.22 (1.01 – 1.46)	–	0.96 (0.89 – 1.04)	0.99 (0.92 – 1.06)
	CV_{intra}	25%	65%	–	27%	25%
37	PE (90% CI)	–	0.93 (0.85 – 1.03)	1.13 (1.04 – 1.23)	–	–
	CV_{intra}		26%	21%		

Midha KK and G McKay
Use of Partial Area Under the Curve for BE Assessment of Products with Complex PK Profiles; a View Point
Meeting of the Pharmaceutical Science and Clinical Pharmacology Advisory Committee, April 13, 2010
http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AdvisoryCommitteeforPharmaceuticalScienceandClinicalPharmacology/UCM209320.pdf

NCA (alternative metrics)

- *pAUC* for multiphasic profiles
  - Methylphenidate SR/ER
    - In fasting subjects the IR's t_{max} is 2 ± 0.5 h ($\overline{x} \pm SD$)
    - 2 hours is also time at which maximal response compared to placebo is achieved
    - By 3 hours, expected that 95 % of patients should achieve maximal early onset of response (since $\overline{x} + 2 \times SD$ = 95 % of population)
    - Food delays IR absorption by about one hour
    - Truncation time point for *pAUC* in fed state therefore is 3 + 2×0.5 = 4 hours

BM Davit (Acting Director Division of Bioequivalence 2, Office of Generic Drugs, OPS/CDER/FDA)
Use of Partial AUC: Case Studies and BE Approaches
Meeting of the Pharmaceutical Science and Clinical Pharmacology Advisory Committee, April 13, 2010
http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AdvisoryCommitteeforPharmaceuticalScienceandClinicalPharmacology/UCM209320.pdf

NCA (alternative metrics)

- *pAUC* for multiphasic profiles
  - Methylphenidate SR/ER
    - Various formulations on the market; hybrid applications (PK + clinical data)
    - Not interchangeable; differences in AUC_{0-4} (fed state)

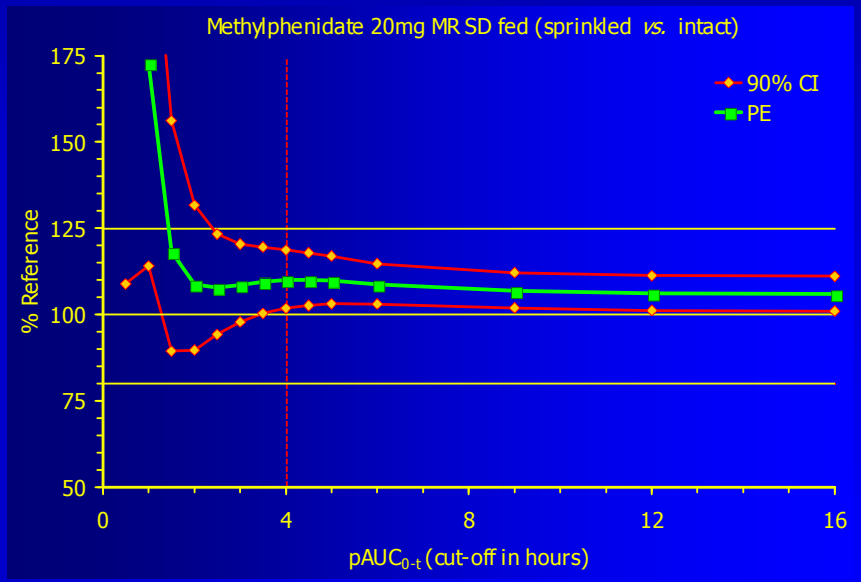
study	AUC_{0-4} (PE, 90% CI)	CV_{intra} (%)
Ritalin LA *vs.* Medikinet ret.[1]	0.804 (0.732 – 0.882)	19.8
Equasym Ret. *vs.* Medikinet ret.[2]	0.829 (0.726 – 0.947)	19.0

1 Haessler F, Tracik F, Dietrich H, Stammer H and J Klatt
A pharmacokinetic study of two modified-release methylphenidate formulations under different food conditions in healthy volunteers
Int J Clin Pharmacol Ther 46/9, 466–76 (2008)

2 Schütz H, Fischer R, Großmann M, Mazur D, Leis HJ and R Ammer
Lack of bioequivalence between two methylphenidate extended modified release formulations in healthy volunteers
Int J Clin Pharmacol Ther 47/12, 761–9 (2009)

NCA (alternative metrics)

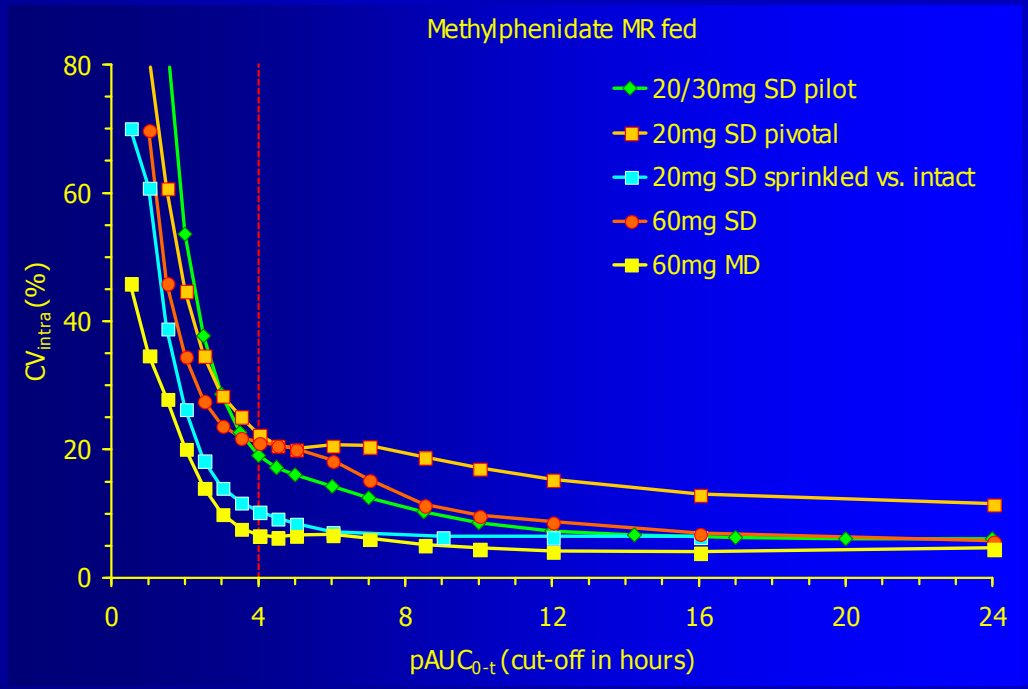
- *pAUC* for multiphasic profiles
  - Methylphenidate SR/ER
    - Although BE, variability of AUC_{0-4} (≈20%) higher than of conventional PK metrics; typical:
      AUC_t 7% – 12%
      C_{max} 10% – 15%



Fischer R, Schütz H, Grossmann M, Leis HJ, and R Ammer
Bioequivalence of a methylphenidate hydrochloride extended-release preparation: comparison of an intact capsule and an opened capsule sprinkled on applesauce
Int J Clin Pharmacol Ther 44/3, 135-141 (2006)

NCA (alternative metrics)

- *pAUC* for multiphasic profiles
  - Methylphenidate SR/ER
    - Variability of early *pAUC* reproducible between studies

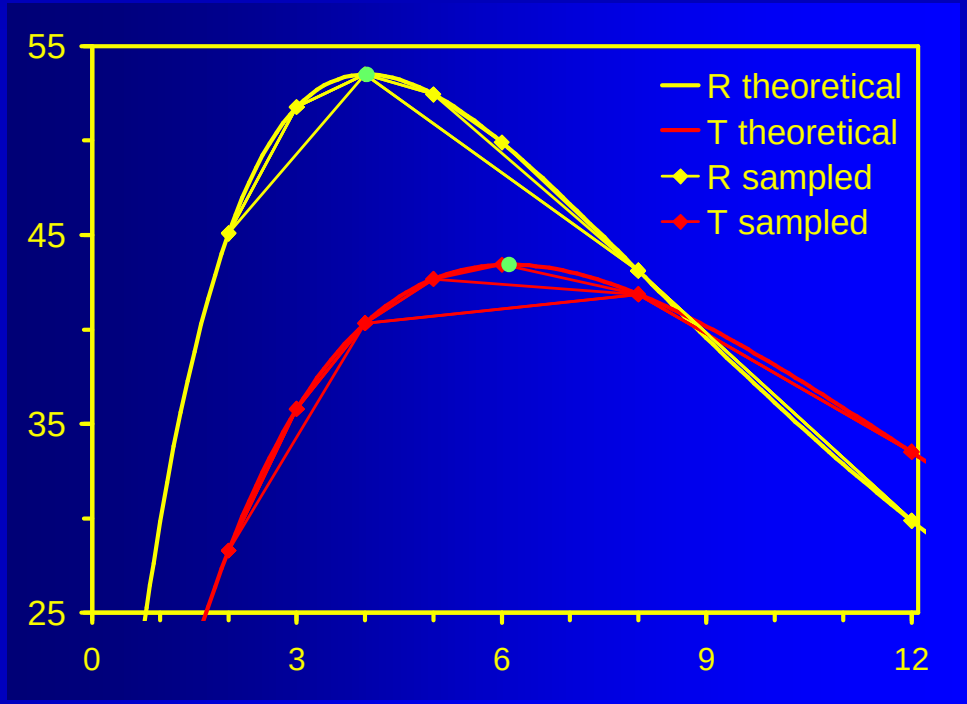


Sampling at C_{max}

- With *any (!)* given sampling scheme the *'true'* C_{max} is missed
  - It is unlikely that we sample *exactly* at the true C_{max} for any given subject
  - High inter- and/or intra-subject variability (single point metric)
  - Variability higher than *AUC's*
  - In many studies the win/loose metric!
  - Try to decrease variability
    - Increase sample size (more subjects)
    - Increase sampling *within* each subject (*maybe* better)

Sampling at C_{max}

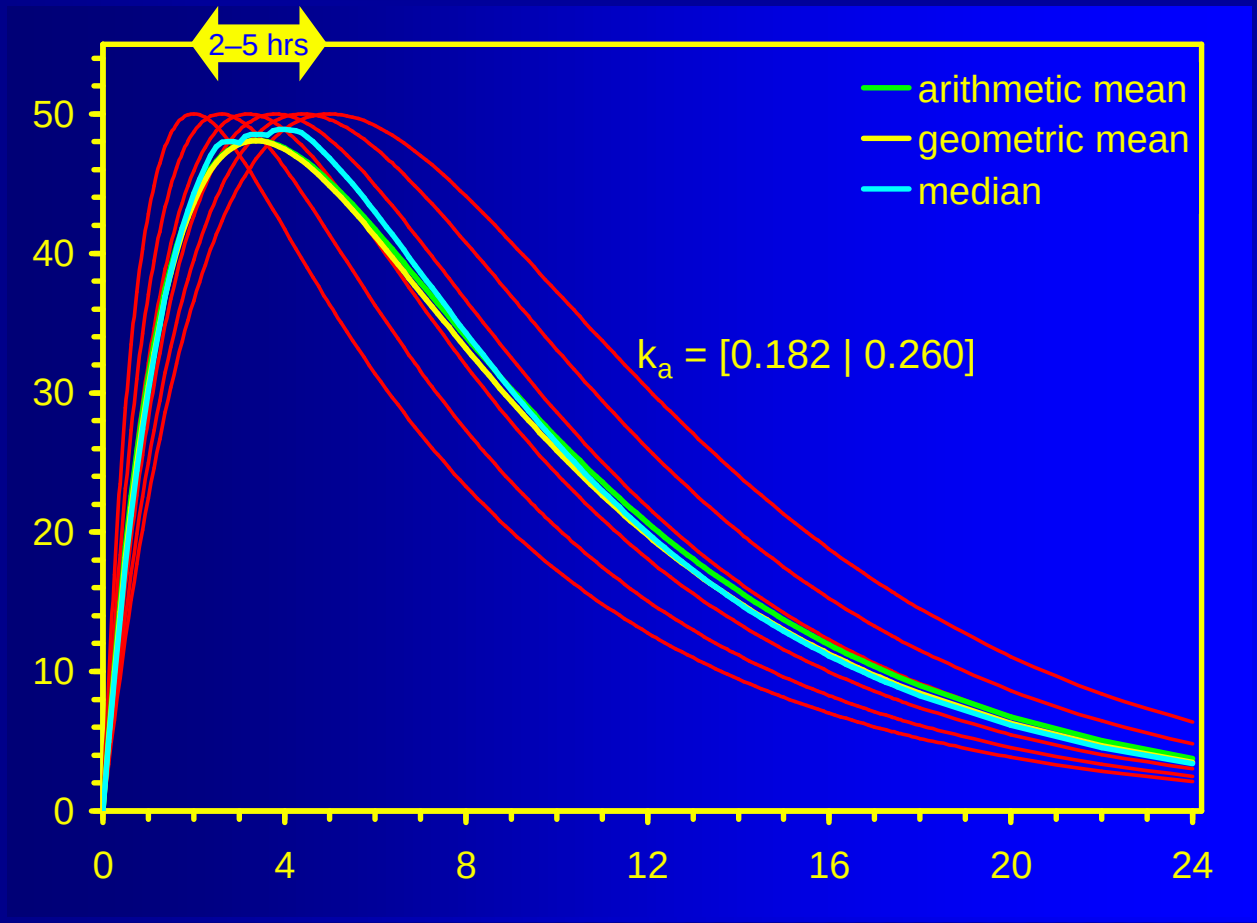
- Theoretical values (from PK simulation)
  C_{max}: 41.9/53.5 (81.2%), t_{max}: 6.11/4.02 (Δ 2.09)
  - # samples [2–12h]
    - n = 4
      - C_{max} 78.3%
      - t_{max} Δ 4
    - n = 5
      - C_{max} 78.3%
      - t_{max} Δ 4
    - n = 6
      - C_{max} 79.8%
      - t_{max} Δ 1
    - n = 7
      - C_{max} 81.2%
      - t_{max} Δ 2



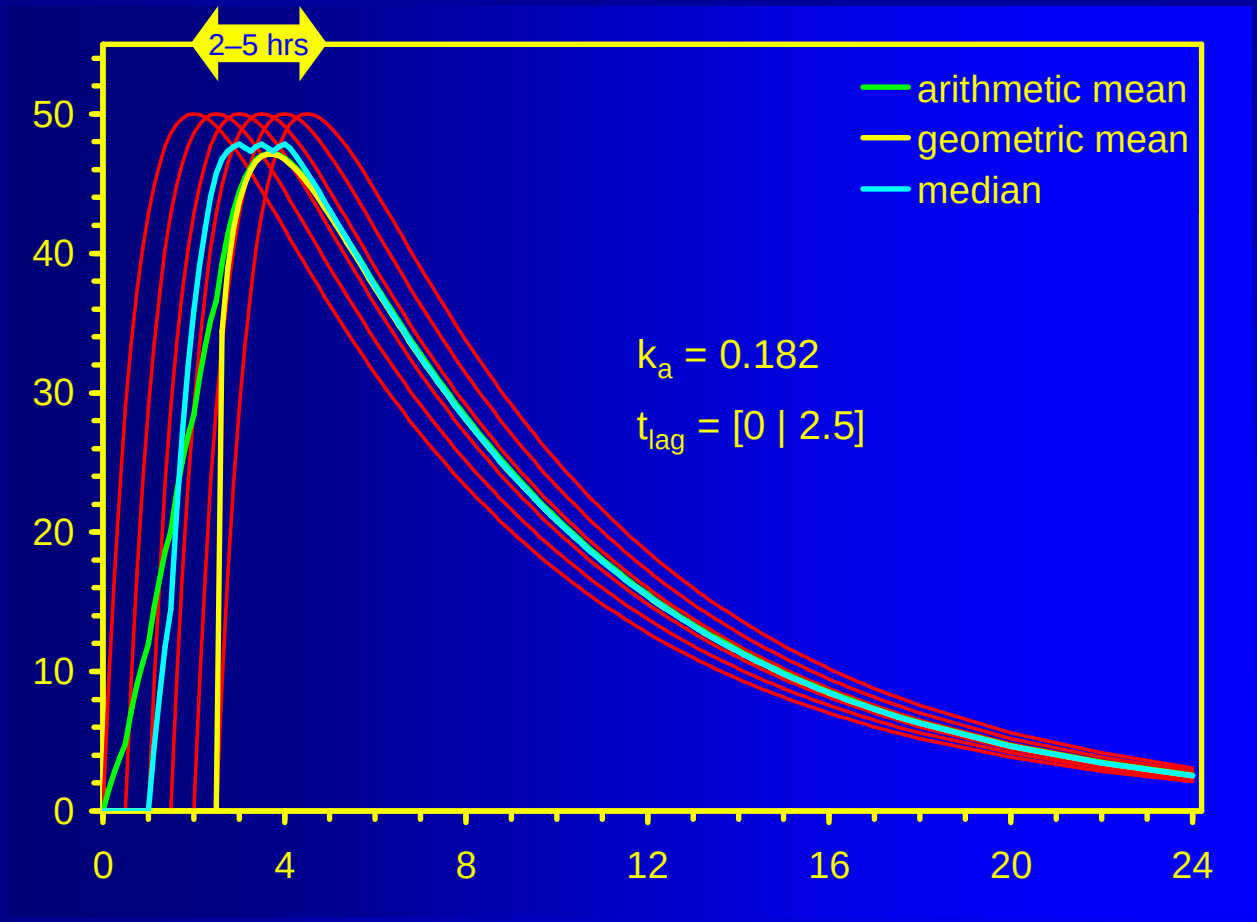
Sampling at C_{max}

- 'C_{max} was observed within two to five hours after administration …'
  - Elimination is drug specific,
  - but what about absorption?
    - Formulation specific (k_a and/or t_{lag})!
    - Dependent on the sampling schedule (in a strict sense study-specific)

Sampling at C_{max}



Sampling at C_{max}



Another Problem

- EMA GL on BE (2010)
  - Section 4.1.8 Reasons for exclusion 1)
    - A subject with lack of any measurable concentrations or only very low plasma concentrations for reference medicinal product. A subject is considered to have very low plasma concentrations if its AUC is less than 5% of reference medicinal product geometric mean AUC (which should be calculated without inclusion of data from the outlying subject). The exclusion of data […] will only be accepted in exceptional cases and may question the validity of the trial.

      Remark: Only possible after unblinding!

Another Problem

- EMA GL on BE (2010)
  - Section 4.1.8 Resons for exclusion 1) cont'd
    - The above can, for immediate release formulations, be the result of subject non-compliance […] and should as far as possible be avoided by mouth check of subjects after intake of study medication to ensure the subjects have swallowed the study medication […]. The samples from subjects excluded from the statistical analysis should still be assayed and the results listed.

Another Problem

- Gastro-resistant (enteric coated) preparations
  - Gastric emptying of single unit dosage forms non-disintegrating in the stomach is prolonged and highly erratic. The consequences of this effect on the enteric coating of delayed release formulations are largely unpredictable.
    - Sampling period should be designed such that measurable concentrations are obtained, taking into consideration not only the half-life of the drug but the possible occurrence of this effect as well. This should reduce the risk of obtaining incomplete concentration-time profiles due to delay to the most possible extent. These effects are highly dependent on individual behaviour.

Another Problem

- Gastro-resistant (enteric coated) preparations
  - Therefore, but only under the conditions that sampling times are designed to identify very delayed absorption and that the incidence of this outlier behaviour is observed with a comparable frequency in both, test and reference products, these incomplete profiles can be excluded from statistical analysis provided that it has been considered in the study protocol.

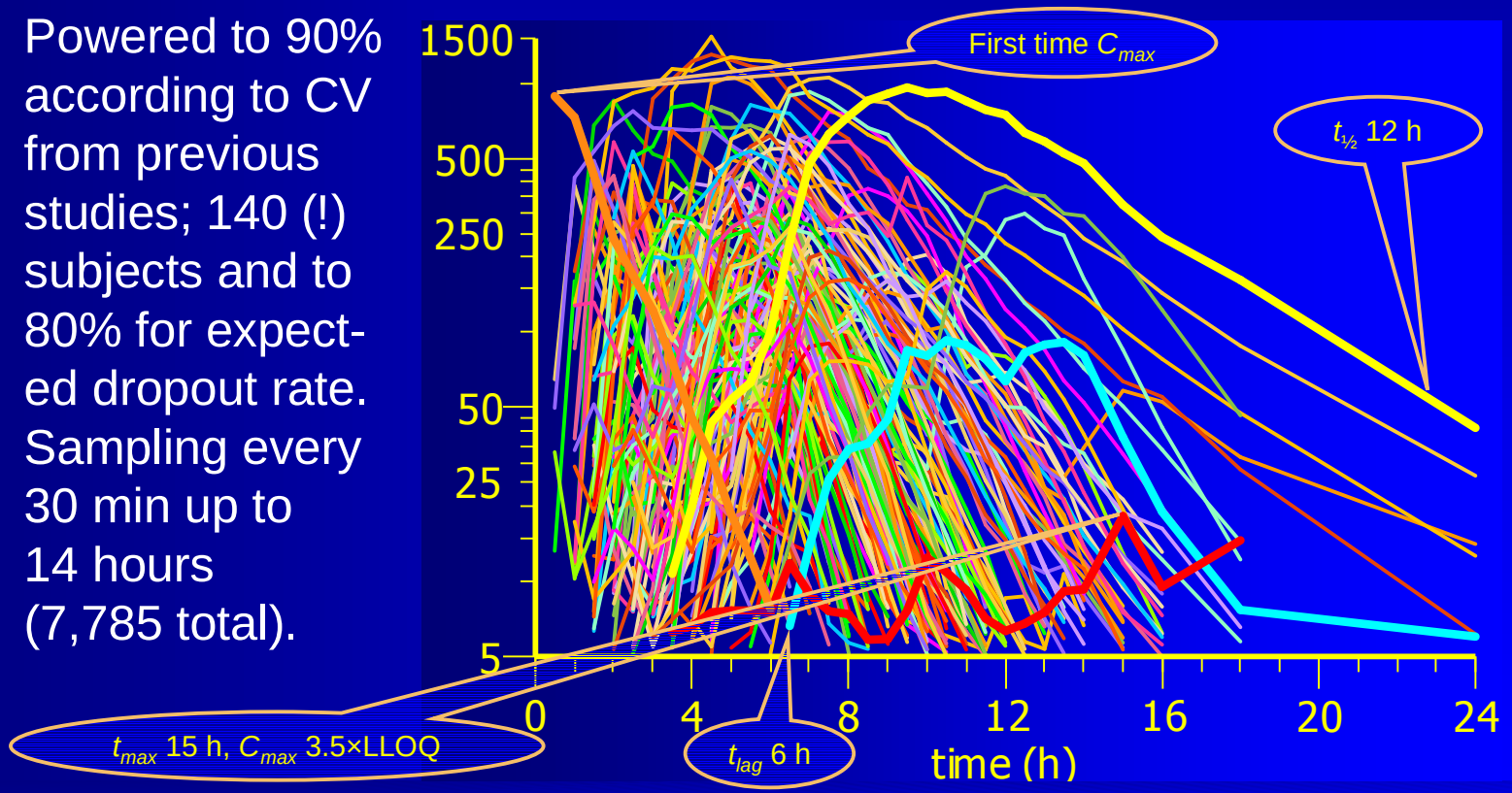
    EMEA, CHMP Efficacy Working Party therapeutic subgroup on Pharmacokinetics (EWP-PK)
    Questions & Answers: Positions on specific questions addressed to the EWP therapeutic subgroup on Pharmacokinetics
    EMEA/618604/2008 Rev. 3, 26 January 2011
    http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500002963.pdf

    What is *'comparable'*? For a study in 24 subjects, we get a significant difference for 5/0 (Fisher's exact test: *p* 0.0496).

Case Study (PPI)

- Attempt to deal with high variability in C_{max}

Powered to 90% according to CV from previous studies; 140 (!) subjects and to 80% for expect-ed dropout rate. Sampling every 30 min up to 14 hours (7,785 total).



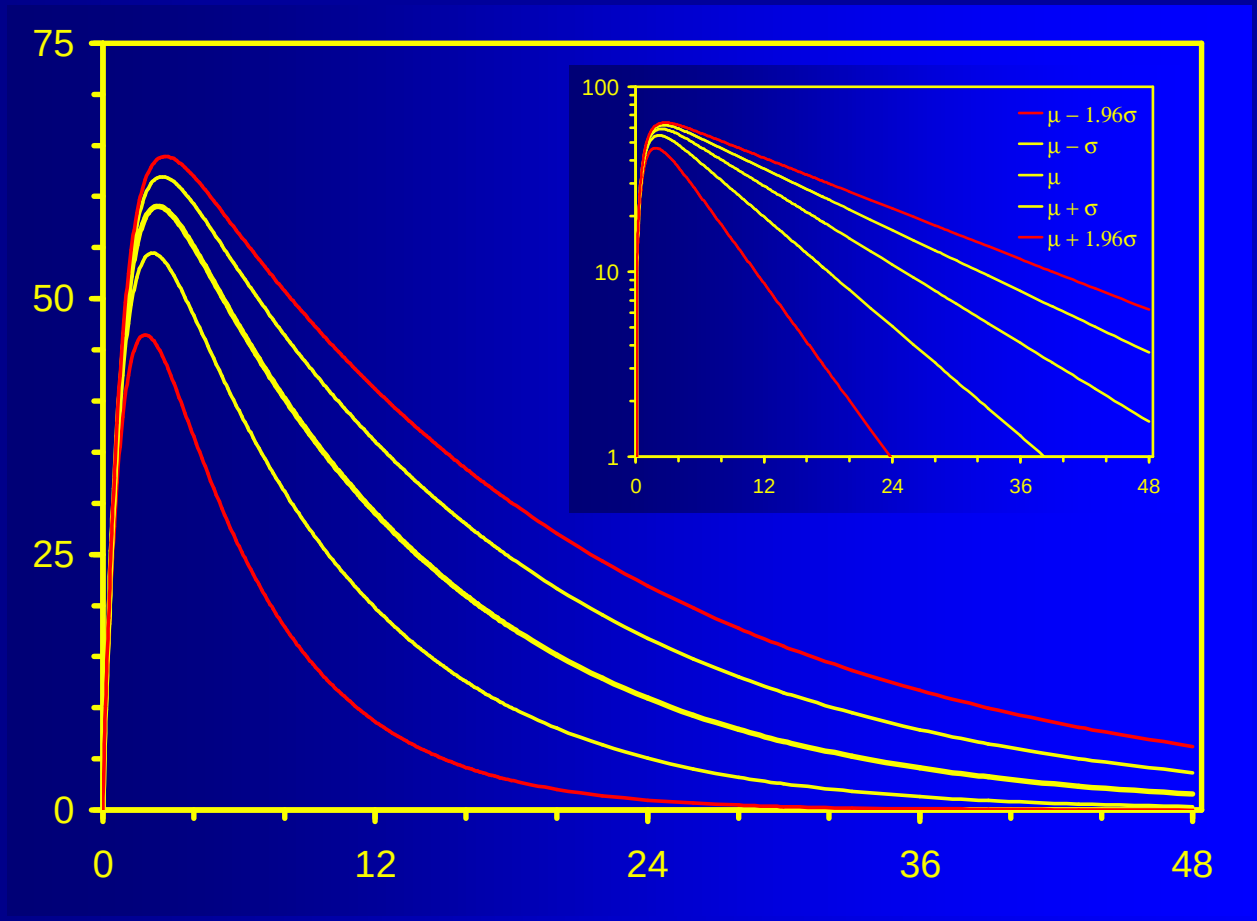
Half lives

- Drug specific, *but* …
  - The *apparent* elimination represents the *slowest* rate constant (controlled release, topicals, transdermals) – *not* necessarily elimination!
  - Avoid the term ‘terminal elimination’ – might not be true
  - Important in designing studies
    - To meet $AUC_t \geq 80\%\ AUC_\infty$ criterion
    - To plan sufficiently long wash-out (avoid carry-over)
    - To plan saturation phase for steady state

Half lives

- Dealing with literature data
  - What if only mean ±SD is given?
    - Assuming normal distribution:
      $\mu \pm \sigma$ covers 68.27% of values (15.87% of values are expected to lie outside of $\mu \pm \sigma$)
    - Example: 8.5 ± 2.4 hours, 36 subjects.
      0.1587 × 36 = 5.71 or in at least five subjects we may expect a half life of > 10.9 hours.
    - Plan for 95% coverage ($z_{0.95}$ = 1.96): $p_{0.95} = \mu \pm z_{0.95} \times \sigma$
      8.5 ± 1.96 × 2.4 = [3.80, 13.2] hours.
      We may expect a half life of >13.2 hours in ~one subject (0.05/2 × 36 = 0.90).

Half lives



Congratulations!
Practically meeting modified release BE requirements
Open Questions?

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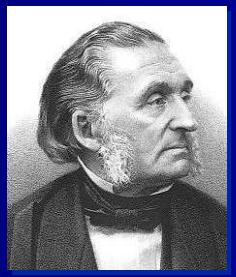
Bioequivalence and Bioavailability Studies
1070 Vienna, Austria
helmut.schuetz@bebac.at

To bear in Remembrance...



You should treat as many patients as possible with the new drugs while they still have the power to heal.

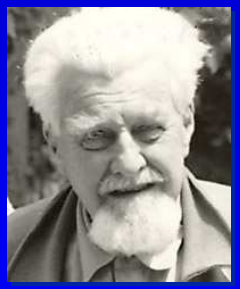
Armand Trousseau

Guidelines
are guidelines
are guidelines.

Henrike Potthast

[…] our greatest mistake would be to forget that data is used for serious decisions in the very real world, and bad information causes suffering and death.

Ben Goldacre



It is a good morning exercise for a research scientist to discard a pet hypothesis every day before breakfast. It keeps him young.

Konrad Lorenz